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(21) International Application Number: PCT/US00/06747 (22) International Filing Date: 15 March 2000 (15.03.00) (30) Priority Data: 60/124,420 15 March 1999 (15.03.99) US (71) Applicant (for all designated States except US): AXYS PHARMACEUTICALS, INC. [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRYANT, Clifford, M. [US/US]; 506 Richmond Drive #4, Millbrae, CA 94030 (US). BUNIN, Barry, A. [US/US]; 171 Elm Avenue, San Bruno, CA 94060 (US). KRAYNACK, Erica, A. [US/US]; Apartment E, 660 Canyon Oaks Drive, Oakland, CA 94605 (US). PATTERSON, John, W. [US/US]; 1619 Montalto Drive, Mountain View, CA 94040 (US). (74) Agents: MONTGOMERY, Wayne, W. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS AS PROTEASE INHIBITORS (57) Abstract The present invention relates to novel <i>N</i> -cyanomethyl amides which are cysteine protease inhibitors, the pharmaceutically acceptable salts and <i>N</i> -oxides thereof, their uses as therapeutic agents and the methods of their making.		

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NOVEL COMPOUNDS AND COMPOSITIONS AS PROTEASE INHIBITORS

THE INVENTION

This application relates to compounds and compositions for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of
5 cathepsins B, K, L or S.

DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the
10 normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increase expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others.
15 For example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

20 The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in osteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

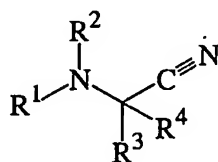
25 Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in

Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogeneic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts.

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which are shown to inhibit the activity of this class of enzymes, in particular molecules which are inhibitors of cathepsins B, K, L and/or S, will be useful as therapeutic agents.

SUMMARY OF THE INVENTION

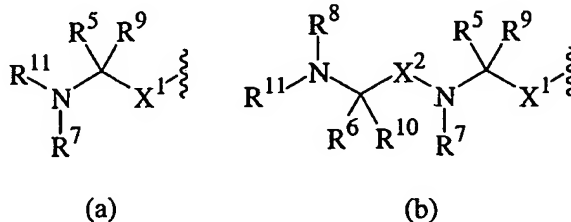
In one particular embodiment, the present invention relates to compounds of Formula (I):



(I)

in which:

R¹ is a group of Formula (a) or (b):



wherein:

X¹ and X² independently are -C(O)- or -CH₂S(O)₂-;

R⁵ and R⁶ are hydrogen or (C₁₋₆)alkyl;

R⁷ and R⁸ are hydrogen or (C₁₋₆)alkyl or as defined below;

R⁹ and R¹⁰ independently are (i) (C₁₋₆)alkyl optionally substituted with cyano, halo or nitro or (ii) a group selected from -X³NR¹²R¹², -X³NR¹²C(O)OR¹²,
 5 -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹²,
 -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR¹²)OR¹²,
 -X³OP(O)(OR¹²)OR¹², -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³, -X³C(O)R¹³,
 -X³C(O)R¹⁴, -X³C(O)OR¹⁴, -X³OC(O)R¹⁴, -X³NR¹⁵C(O)R¹⁴, -X³NR¹⁵C(O)OR¹⁴,
 -X³C(O)NR¹⁴R¹⁵, -X³S(O)₂NR¹⁴R¹⁵, -X³NR¹⁵C(O)NR¹⁴R¹⁵,
 10 -X³NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴OR¹⁴, or
 -X⁴NR¹⁴R¹⁵, wherein X³ is (C₁₋₆)alkylene, X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each
 occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³
 is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 15 (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is
 hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶,
 -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶,
 20 -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or
 -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or
 (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (iii) a group selected from
 25 (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl,
 hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶,

-X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶,
 -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or
 -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein
 within R⁹ and/or R¹⁰ any alicyclic or aromatic ring system present may be substituted
 5 further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene,
 cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹²,
 -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹²,
 -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR⁴)OR¹²,
 -X⁴OP(O)(OR¹²)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³
 10 and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁹ taken together with R⁷ and/or R¹⁰ taken together with R⁸ form
 trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with
 hydroxy, oxo or methylene; and

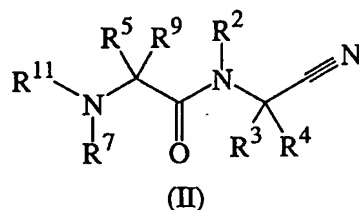
R¹¹ is -X⁵X⁶R¹⁸, wherein X⁵ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁶ is a
 15 bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is
 (i) (C₁₋₁₀)alkyl optionally substituted by cyano, halo, nitro, -NR¹²R¹²,
 -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹²,
 -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -P(O)(OR¹²)OR¹²,
 -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -OR²⁰, -SR²⁰,
 20 -S(O)R²⁰, -S(O)₂R²⁰, -C(O)R²⁰, -C(O)OR²⁰, -C(O)NR²⁰R²¹, -NR²⁰R²¹,
 -NR²¹C(O)R²⁰, -NR²¹C(O)OR²⁰, -NR²¹C(O)NR²⁰R²¹ or -NR²¹C(NR²¹)NR²⁰R²¹,
 wherein R¹² and R¹³ are as defined above, R²⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²¹ at each
 25 occurrence independently is hydrogen or (C₁₋₆)alkyl, or
 (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl,

- wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by
 $-X^4OR^{22}$, $-X^4SR^{22}$, $-X^4S(O)R^{22}$, $-X^4S(O)_2R^{22}$, $-X^4C(O)R^{22}$, $-X^4C(O)OR^{22}$,
 $-X^4C(O)NR^{22}R^{23}$, $-X^4NR^{22}R^{23}$, $-X^4NR^{23}C(O)R^{22}$, $-X^4NR^{23}C(O)OR^{22}$,
 $-X^4NR^{23}C(O)NR^{22}R^{23}$ or $-X^4NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^4 is as defined
5 above, R^{22} is (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl,
phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence
independently is hydrogen or (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic
ring system present may be substituted further by 1 to 5 radicals independently
selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl,
10 nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$,
 $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$,
 $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$,
 $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and
 R^{13} are as defined above;
15 R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;
 R^3 is hydrogen, (C_{1-6}) alkyl or as defined below; and
 R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl is optionally substituted with
cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$,
20 $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$,
 $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$,
 $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or
 $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} , R^{13} , R^{14} and R^{15} are as defined above, or (ii) a group
selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
25 (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and
hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$,
 $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$,

-X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷,
 wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or
 aromatic ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro,
 5 -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹²,
 -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹²,
 -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³,
 -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁴ and R² taken together form trimethylene, tetramethylene or
 10 phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or
 R⁴ and R³ together with the carbon atom to which both R⁴ and R³ are attached form
 (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene; and the *N*-oxide derivatives, prodrug
 derivatives, protected derivatives, individual isomers and mixtures of isomers; and the
 pharmaceutically acceptable salts thereof.

15 In another particular embodiment, this invention relates to compounds of Formula (II):



wherein:

R² is hydrogen or (C₁₋₆)alkyl or as defined below;

R³ is hydrogen, (C₁₋₆)alkyl or as defined below;

20 R⁴ is (i) hydrogen or (C₁₋₆)alkyl, wherein said alkyl optionally is substituted with
 cyano, halo, nitro, -NR¹²R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹²,
 -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹²,
 -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³,
 -OR¹⁴, -SR¹⁴, -S(O)R¹⁴, -S(O)₂R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, -OC(O)R¹⁴, -NR¹⁴R¹⁵,
 25 -NR¹⁵C(O)R¹⁴, -NR¹⁵C(O)OR¹⁴, -C(O)NR¹⁴R¹⁵, -S(O)₂NR¹⁴R¹⁵, -NR¹⁵C(O)NR¹⁴R¹⁵ or

- NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, wherein R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
- 5 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or
- 10 -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (ii) a group selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl,
- 15 hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶,
- 20 -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁴ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹²,
- 25 -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁴ and R² taken together form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or

R^4 and R^3 together with the carbon atom to which both R^4 and R^3 are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

R^5 is hydrogen or (C₁₋₆)alkyl;

R^7 is hydrogen or (C₁₋₆)alkyl;

- 5 R^9 is (C₆₋₁₂)aryl(C₁₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₁₋₆)alkyl, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$ or $-X^4NR^{14}R^{15}$, wherein X^4 , R^{14} and R^{15} are as defined above and wherein within R^9 said aryl or heteroaryl ring optionally is substituted by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)R^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$, wherein X^4 , R^{12} and R^{13} are as defined above; and

- R^{11} is $-X^5X^6R^{18}$, wherein X^5 is $-C(O)-$, $-C(O)C(O)-$ or $-S(O)_2-$, X^6 is a bond, $-O-$ or $-NR^{19}-$, wherein R^{19} is hydrogen or (C₁₋₆)alkyl, and R^{18} is (i) (C₁₋₁₀)alkyl optionally substituted by cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-OR^{20}$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-NR^{20}R^{21}$, $-NR^{21}C(O)R^{20}$, $-NR^{21}C(O)OR^{20}$, $-NR^{21}C(O)NR^{20}R^{21}$ or $-NR^{21}C(NR^{21})NR^{20}R^{21}$, wherein
- 15 R^{12} and R^{13} are as defined above, R^{20} is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R^{21} at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or
- 25 (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by $-X^4OR^{22}$, $-X^4SR^{22}$, $-X^4S(O)R^{22}$, $-X^4S(O)_2R^{22}$, $-X^4C(O)R^{22}$, $-X^4C(O)OR^{22}$, $-X^4C(O)NR^{22}R^{23}$, $-X^4NR^{22}R^{23}$, $-X^4NR^{23}C(O)R^{22}$, $-X^4NR^{23}C(O)OR^{22}$,

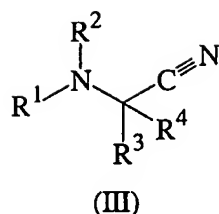
$-X^4NR^{23}C(O)NR^{22}R^{23}$ or $-X^4NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^4 is as defined above, R^{22} is
 (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or
hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence independently is hydrogen or
 (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic ring system present may be substituted
5 further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano,
halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$,
 $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$,
 $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$,
 $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 ,
10 R^{12} and R^{13} are as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected
derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable
salts thereof.

In another particular embodiment, the present invention relates to a pharmaceutical
composition which contains a compound of Formula I or a *N*-oxide derivative, prodrug
15 derivative, individual isomer or mixture of isomers or a pharmaceutically acceptable salt
thereof in admixture with one or more suitable excipients.

In another particular embodiment, the present invention relates to a method of treating
a disease in an animal in which inhibition of a cysteine protease can prevent, inhibit or
ameliorate the pathology and/or symptomatology of the disease, which method comprises
20 administering to the animal a therapeutically effective amount of compound of Formula I or a
N-oxide derivative, prodrug derivative, individual isomer or mixture of isomers or a
pharmaceutically acceptable salt thereof.

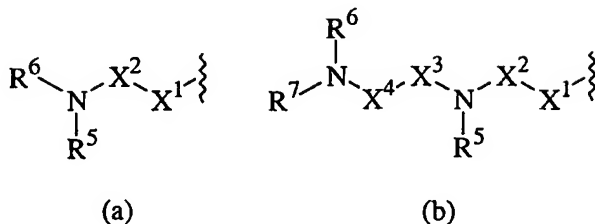
In another particular embodiment, the present invention relates processes for
preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivative, protected
25 derivatives, individual isomers and mixtures of isomers, and the pharmaceutically acceptable
salts thereof as set forth in "Detailed Description of the Invention".

In another particular embodiment, the present invention relates a compound of
Formula (III):



in which:

R¹ is a group of Formula (a) or (b):



5 wherein:

X¹ and X³ independently are -C(O)- or -S(O)₂-,

X² is -CR⁸R⁹-, -CH₂CR⁸R⁹- or -CR⁸R⁹CH₂- and X⁴ is -CHR¹⁰-,
-CH₂CHR¹⁰- or -CHR¹⁰CH₂-, wherein:

R⁸ is hydrogen or (C₁₋₆)alkyl,

- 10 R⁹ is (i) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl optionally substituted with -OR¹¹, -SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)R¹¹, -C(O)OR¹¹, -NR¹¹R¹², -NR¹²C(O)OR¹¹, -C(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², -NR¹²C(O)NR¹¹R¹² or -NR¹²C(NR¹²)NR¹¹R¹², wherein R¹¹ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl,
- 15 (C₆₋₁₂)aryl(C₀₋₃)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl and R¹² is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl optionally substituted with -R¹³,
- 20 -X⁵OR¹³, -X⁵SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -C(O)OR¹³, -X⁵NR¹³R¹⁴, -X⁵NR¹⁴C(O)OR¹³, -C(O)NR¹³R¹⁴, -S(O)₂NR¹³R¹⁴, -NR¹⁴C(O)NR¹³R¹⁴ or -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein X⁵ is a bond or

methylene, R^{13} is $(C_{3-12})\text{cycloalkyl}(C_{0-3})\text{alkyl}$,
 hetero $(C_{3-12})\text{cycloalkyl}(C_{0-3})\text{alkyl}$, $(C_{6-12})\text{aryl}(C_{0-3})\text{alkyl}$,
 hetero $(C_{5-12})\text{aryl}(C_{0-3})\text{alkyl}$, $(C_{9-12})\text{polycycloaryl}(C_{0-3})\text{alkyl}$ or
 hetero $(C_{8-12})\text{polycycloaryl}(C_{0-3})\text{alkyl}$ and R^{14} is hydrogen or $(C_{1-6})\text{alkyl}$, or
 5 (iii) together with R^5 when X^2 is $-\text{CHR}^9-$ forms trimethylene, tetramethylene or
 phenylene-1,2-dimethylene, optionally substituted with 1 to 2 of hydroxy,
 oxo, $(C_{1-4})\text{alkyl}$ or methylene; wherein any 1 to 3 annular atoms of any
 aromatic ring with available valences comprising R^9 are optionally
 independently substituted with halo, nitro, cyano, $(C_{1-6})\text{alkyl}$,
 10 halo-substituted $(C_{1-6})\text{alkyl}$, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$,
 $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{OR}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$ or
 $-\text{X}^5\text{NR}^{15}\text{C}(\text{NR}^{15}\text{NR}^{15}\text{R}^{15})$, wherein X^5 is as defined above and each R^{15}
 independently is hydrogen or $(C_{1-6})\text{alkyl}$, and
 R^{10} is hydrogen or $(C_{1-4})\text{alkyl}$;
 15 R^5 and R^7 are independently hydrogen, $(C_{1-6})\text{alkyl}$ or as defined above; and
 R^6 is $-\text{X}^6\text{X}^7\text{R}^{16}$, wherein X^6 is $-\text{C}(\text{O})-$ or $-\text{S}(\text{O})_2-$, X^7 is a bond, $-\text{O}-$ or
 $-\text{NR}^{17}-$, wherein R^{17} is hydrogen or $(C_{1-6})\text{alkyl}$, and R^{16} is (i) $(C_{1-6})\text{alkyl}$ or
 halo-substituted $(C_{1-6})\text{alkyl}$ optionally substituted with $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$,
 $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{11}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$,
 20 $-\text{NR}^{12}\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$ or $-\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{11}\text{R}^{12}$, wherein R^{11} and R^{12} are as defined
 above, or (ii) $(C_{3-6})\text{cycloalkyl}(C_{0-3})\text{alkyl}$, hetero $(C_{3-6})\text{cycloalkyl}(C_{0-3})\text{alkyl}$,
 $(C_{6-12})\text{aryl}(C_{0-3})\text{alkyl}$, hetero $(C_{5-12})\text{aryl}(C_{0-3})\text{alkyl}$, $(C_{9-12})\text{polycycloaryl}(C_{0-3})\text{alkyl}$ or
 hetero $(C_{8-12})\text{polycycloaryl}(C_{0-3})\text{alkyl}$ optionally substituted with 1 to 2 of $-\text{R}^{13}$,
 $-\text{X}^5\text{OR}^{13}$, $-\text{X}^5\text{SR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{X}^5\text{NR}^{13}\text{R}^{14}$,
 25 $-\text{X}^5\text{NR}^{14}\text{C}(\text{O})\text{OR}^{13}$, $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$ or
 $-\text{NR}^{14}\text{C}(\text{NR}^{14})\text{NR}^{13}\text{R}^{14}$, wherein X^5 , R^{13} and R^{14} are as defined above; wherein any
 1 to 3 annular atoms of any aromatic ring with available valences comprising R^{16}
 optionally independently are substituted with halo, nitro, cyano, $(C_{1-6})\text{alkyl}$,
 halo-substituted $(C_{1-6})\text{alkyl}$, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$,

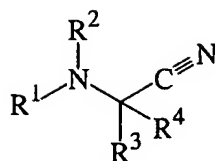
$-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{OR}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$ or $-\text{X}^5\text{NR}^{15}\text{C}(\text{NR}^{15})\text{NR}^{15}\text{R}^{15}$, wherein X^5 and R^{15} are as defined above;

R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;

R^3 is hydrogen, (C_{1-10}) alkyl or as defined below; and

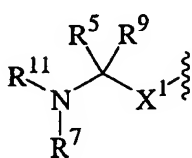
- 5 R^4 is (i) hydrogen, (ii) (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl optionally substituted with $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{11}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$ or $-\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{11}\text{R}^{12}$, wherein R^{11} and R^{12} are as defined above, or (iii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) polycycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) polycycloaryl (C_{0-3}) alkyl optionally substituted with $-\text{R}^{13}$, $-\text{X}^5\text{OR}^{13}$, $-\text{X}^5\text{SR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{X}^5\text{NR}^{13}\text{R}^{14}$, $-\text{X}^5\text{NR}^{14}\text{C}(\text{O})\text{OR}^{13}$, $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$ or $-\text{NR}^{14}\text{C}(\text{NR}^{14})\text{NR}^{13}\text{R}^{14}$, wherein X^5 , R^{13} and R^{14} are as defined above or (iv) together with R^2 forms trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo, (C_{1-4}) alkyl or methylene or (v) together with R^3 forms ethylene, trimethylene or tetramethylene; wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R^4 optionally independently are substituted with halo, nitro, cyano, (C_{1-6}) alkyl, halo-substituted (C_{1-6}) alkyl, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$, $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{OR}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$ or $-\text{X}^5\text{NR}^{15}\text{C}(\text{NR}^{15})\text{NR}^{15}\text{R}^{15}$, wherein X^5 and R^{15} are as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

In another particular embodiment, the present invention relates to a method of treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or
 25 symptomatology of the disease, which method comprising administering to the animal a therapeutically effective amount of a compound of Formula (I):

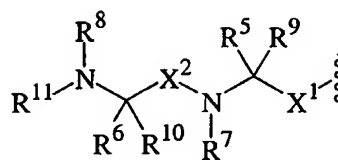


(I)

in which:

R¹ is a group of Formula (a) or (b):

(a)



(b)

5 wherein:

X¹ and X² independently are -C(O)- or -CH₂S(O)₂-;R⁵ and R⁶ are hydrogen or (C₁₋₆)alkyl;R⁷ and R⁸ are hydrogen or (C₁₋₆)alkyl or as defined below;R⁹ and R¹⁰ independently are (i) (C₁₋₆)alkyl optionally substituted with cyano,10 halo or nitro or (ii) a group selected from -X³NR¹²R¹³, -X³NR¹²C(O)OR¹²,-X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹²,-X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR¹²)OR¹²,-X³OP(O)(OR¹²)OR¹², -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³, -X³C(O)R¹³,-X³C(O)R¹⁴, -X³C(O)OR¹⁴, -X³OC(O)R¹⁴, -X³NR¹⁵C(O)R¹⁴, -X³NR¹⁵C(O)OR¹⁴,15 -X³C(O)NR¹⁴R¹⁵, -X³S(O)₂NR¹⁴R¹⁵, -X³NR¹⁵C(O)NR¹⁴R¹⁵,-X³NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴OR¹⁴, or-X⁴NR¹⁴R¹⁵, wherein X³ is (C₁₋₆)alkylene, X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,20 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,(C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is

- hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (iii) a group selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR⁴)OR¹², -X⁴OP(O)(OR¹²)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or
- R⁹ taken together with R⁷ and/or R¹⁰ taken together with R⁸ form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene; and
- R¹¹ is -X⁵X⁶R¹⁸, wherein X⁵ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁶ is a bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is

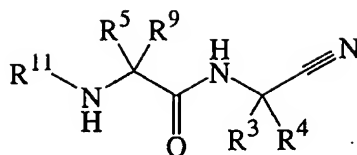
- (i) (C_{1-10}) alkyl optionally substituted by cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-OR^{20}$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-NR^{20}R^{21}$, $-NR^{21}C(O)R^{20}$, $-NR^{21}C(O)OR^{20}$, $-NR^{21}C(O)NR^{20}R^{21}$ or $-NR^{21}C(NR^{21})NR^{20}R^{21}$, wherein R^{12} and R^{13} are as defined above, R^{20} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-6}) alkyl and R^{21} at each occurrence independently is hydrogen or (C_{1-6}) alkyl, or
- (ii) (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-6}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by $-X^4OR^{22}$, $-X^4SR^{22}$, $-X^4S(O)R^{22}$, $-X^4S(O)_2R^{22}$, $-X^4C(O)R^{22}$, $-X^4C(O)OR^{22}$, $-X^4C(O)NR^{22}R^{23}$, $-X^4NR^{22}R^{23}$, $-X^4NR^{23}C(O)R^{22}$, $-X^4NR^{23}C(O)OR^{22}$, $-X^4NR^{23}C(O)NR^{22}R^{23}$ or $-X^4NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^4 is as defined above, R^{22} is (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence independently is hydrogen or (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and R^{13} are as defined above;
- R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;

R^3 is hydrogen, (C_{1-6}) alkyl or as defined below; and

- R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl is optionally substituted with cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$, $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} , R^{13} , R^{14} and R^{15} are as defined above, or (ii) a group selected from (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, (C_{6-12}) aryl, (C_{0-6}) alkyl, hetero (C_{5-12}) aryl, (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl, (C_{0-6}) alkyl and hetero (C_{8-12}) polycycloaryl, (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein X^4 , R^{16} and R^{17} are as defined above; wherein within R^9 and/or R^{10} any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and R^{13} are as defined above, or

R^4 and R^2 taken together form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or

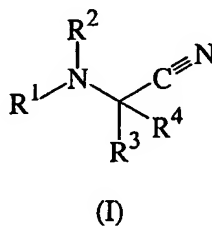
- R^4 and R^3 together with the carbon atom to which both R^4 and R^3 are attached form (C_{3-8}) cycloalkylene or (C_{3-8}) heterocycloalkylene; or an *N*-oxide derivative, prodrug derivative, individual isomer and mixtures of isomers; or a pharmaceutically acceptable salt thereof, but excluding compounds of the formula



in which R^3 and R^4 are each hydrogen or (C_{1-6}) alkyl, or together with the carbon atom to which they are both attached form (C_{3-5}) cycloalkylene; R^5 is hydrogen or (C_{1-6}) alkyl; R^9 is (C_{6-12}) aryl (C_{1-6}) alkyl, hetero (C_{5-12}) aryl (C_{1-6}) alkyl, (C_{4-5}) alkyl or cyclohexylmethyl; and R^{11} is

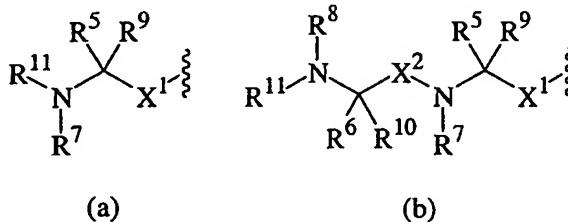
5 $C(O)R^{18}$ wherein R^{18} is hetero (C_{3-12}) cycloalkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl.

In another particular embodiment, the present invention relates to the use of a compound of Formula (I):



10 in which:

R^1 is a group of Formula (a) or (b):



wherein:

X^1 and X^2 independently are $-C(O)-$ or $-CH_2S(O)_2-$;

15 R^5 and R^6 are hydrogen or (C_{1-6}) alkyl;

R^7 and R^8 are hydrogen or (C_{1-6}) alkyl or as defined below;

R^9 and R^{10} independently are (i) (C_{1-6}) alkyl optionally substituted with cyano, halo or nitro or (ii) a group selected from $-X^3NR^{12}R^{12}$, $-X^3NR^{12}C(O)OR^{12}$, $-X^3NR^{12}C(O)NR^{12}R^{12}$, $-X^3NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^3OR^{12}$, $-X^3SR^{12}$, $-X^3C(O)OR^{12}$, $-X^3C(O)NR^{12}R^{12}$, $-X^3S(O)_2NR^{12}R^{12}$, $-X^3P(O)(OR^{12})OR^{12}$, $-X^3OP(O)(OR^{12})OR^{12}$, $-X^3NR^{12}C(O)R^{13}$, $-X^3S(O)R^{13}$, $-X^3S(O)_2R^{13}$, $-X^3C(O)R^{13}$, $-X^3C(O)R^{14}$, $-X^3C(O)OR^{14}$, $-X^3OC(O)R^{14}$, $-X^3NR^{15}C(O)R^{14}$, $-X^3NR^{15}C(O)OR^{14}$, $-X^3C(O)NR^{14}R^{15}$, $-X^3S(O)_2NR^{14}R^{15}$, $-X^3NR^{15}C(O)NR^{14}R^{15}$, $-X^3NR^{15}C(NR^{15})NR^{14}R^{15}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4OR^{14}$, or $-X^4NR^{14}R^{15}$, wherein X^3 is (C_{1-6}) alkylene, X^4 is a bond or (C_{1-6}) alkylene, R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl, R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl, R^{14} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl and R^{15} is hydrogen or (C_{1-6}) alkyl, and wherein within R^{14} said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein X^4 is a bond or (C_{1-6}) alkylene, R^{16} is hydrogen or (C_{1-6}) alkyl and R^{17} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, or (iii) a group selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or

-X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹²,
 5 -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹²,
 -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR⁴)OR¹²,
 -X⁴OP(O)(OR¹²)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³
 and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁹ taken together with R⁷ and/or R¹⁰ taken together with R⁸ form
 10 trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene; and

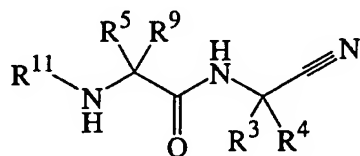
R¹¹ is -X⁵X⁶R¹⁸, wherein X⁵ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁶ is a bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is
 (i) (C₁₋₁₀)alkyl optionally substituted by cyano, halo, nitro, -NR¹²R¹²,
 15 -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹²,
 -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -P(O)(OR¹²)OR¹²,
 -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -OR²⁰, -SR²⁰,
 -S(O)R²⁰, -S(O)₂R²⁰, -C(O)R²⁰, -C(O)OR²⁰, -C(O)NR²⁰R²¹, -NR²⁰R²¹,
 -NR²¹C(O)R²⁰, -NR²¹C(O)OR²⁰, -NR²¹C(O)NR²⁰R²¹ or -NR²¹C(NR²¹)NR²⁰R²¹,
 20 wherein R¹² and R¹³ are as defined above, R²⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²¹ at each
 occurrence independently is hydrogen or (C₁₋₆)alkyl, or
 (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 25 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl,
 wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by
 -X⁴OR²², -X⁴SR²², -X⁴S(O)R²², -X⁴S(O)₂R²², -X⁴C(O)R²², -X⁴C(O)OR²²,

- $-X^4C(O)NR^{22}R^{23}$, $-X^4NR^{22}R^{23}$, $-X^4NR^{23}C(O)R^{22}$, $-X^4NR^{23}C(O)OR^{22}$,
 $-X^4NR^{23}C(O)NR^{22}R^{23}$ or $-X^4NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^4 is as defined
 above, R^{22} is (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl,
 phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence
 5 independently is hydrogen or (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic
 ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl,
 nitro, $-X^4NR^{12}R^{13}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{13}$,
 $-X^4NR^{12}C(NR^{13})NR^{12}R^{13}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{13}$,
 10 $-X^4S(O)_2NR^{12}R^{13}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$,
 $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and
 R^{13} are as defined above;
 R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;
 R^3 is hydrogen, (C_{1-6}) alkyl or as defined below; and
 15 R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl is optionally substituted with
 cyano, halo, nitro, $-NR^{12}R^{13}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{13}$,
 $-NR^{12}C(NR^{13})NR^{12}R^{13}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{13}$, $-S(O)_2NR^{12}R^{13}$,
 $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$,
 $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$,
 20 $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or
 $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} , R^{13} , R^{14} and R^{15} are as defined above, or (ii) a group
 selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and
 hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 25 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
 selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$,
 $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$,
 $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$,
 wherein X^4 , R^{16} and R^{17} are as defined above; wherein within R^9 and/or R^{10} any alicyclic or

aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹²,
 5 -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

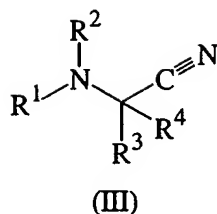
R⁴ and R² taken together form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or

R⁴ and R³ together with the carbon atom to which both R⁴ and R³ are attached form
 10 (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene; or an *N*-oxide derivative, prodrug derivative, individual isomer and mixtures of isomers; or a pharmaceutically acceptable salt thereof, but excluding compounds of the formula



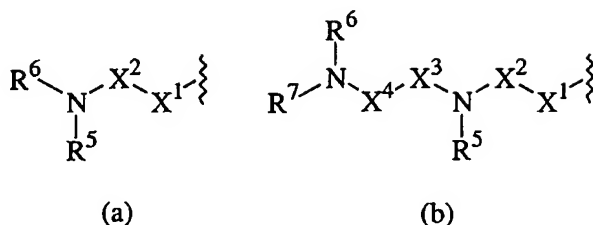
in which R³ and R⁴ are each hydrogen or (C₁₋₆)alkyl, or together with the carbon atom to
 15 which they are both attached form (C₃₋₅)cycloalkylene; R⁵ is hydrogen or (C₁₋₆)alkyl; R⁹ is (C₆₋₁₂)aryl(C₁₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₁₋₆)alkyl, (C₄₋₅)alkyl or cyclohexylmethyl; and R¹¹ is C(O)R¹⁸ wherein R¹⁸ is hetero(C₃₋₁₂)cycloalkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, in the manufacture of a medicament for treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease.

20 In another particular embodiment, the present invention relates to a method of treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease, which method comprising administering to the animal a therapeutically effective amount of a compound of Formula (III):



in which:

R¹ is a group of Formula (a) or (b):



5 wherein:

X¹ and X³ independently are -C(O)- or -S(O)₂-,

X² is -CR⁸R⁹-, -CH₂CR⁸R⁹- or -CR⁸R⁹CH₂- and X⁴ is -CHR¹⁰-,
-CH₂CHR¹⁰- or -CHR¹⁰CH₂-, wherein:

R⁸ is hydrogen or (C₁₋₆)alkyl,

- 10 R⁹ is (i) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl optionally substituted with -OR¹¹, -SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)R¹¹, -C(O)OR¹¹, -NR¹¹R¹², -NR¹²C(O)OR¹¹, -C(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², -NR¹²C(O)NR¹¹R¹² or -NR¹²C(NR¹³)NR¹¹R¹², wherein R¹¹ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl,
- 15 (C₆₋₁₂)aryl(C₀₋₃)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl and R¹² is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl optionally substituted with -R¹³,
- 20 -X⁵OR¹³, -X⁵SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -C(O)OR¹³, -X⁵NR¹³R¹⁴, -X⁵NR¹⁴C(O)OR¹³, -C(O)NR¹³R¹⁴, -S(O)₂NR¹³R¹⁴, -NR¹⁴C(O)NR¹³R¹⁴ or -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein X⁵ is a bond or

methylene, R^{13} is (C_{3-12}) cycloalkyl (C_{0-3}) alkyl,
 hetero (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl,
 hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) polycycloaryl (C_{0-3}) alkyl or
 hetero (C_{8-12}) polycycloaryl (C_{0-3}) alkyl and R^{14} is hydrogen or (C_{1-6}) alkyl, or
 5 (iii) together with R^5 when X^2 is $-CHR^9-$ forms trimethylene, tetramethylene or
 phenylene-1,2-dimethylene, optionally substituted with 1 to 2 of hydroxy,
 oxo, (C_{1-4}) alkyl or methylene; wherein any 1 to 3 annular atoms of any
 aromatic ring with available valences comprising R^9 are optionally
 independently substituted with halo, nitro, cyano, (C_{1-6}) alkyl,
 10 halo-substituted (C_{1-6}) alkyl, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{15}$,
 $-S(O)_2NR^{15}R^{15}$, $-X^5NR^{15}R^{15}$, $-X^5NR^{15}C(O)OR^{15}$, $-X^5NR^{15}C(O)NR^{15}R^{15}$ or
 $-X^5NR^{15}C(NR^{15}NR^{15}R^{15})$, wherein X^5 is as defined above and each R^{15}
 independently is hydrogen or (C_{1-6}) alkyl, and
 R^{10} is hydrogen or (C_{1-4}) alkyl;
 15 R^5 and R^7 are independently hydrogen, (C_{1-6}) alkyl or as defined above; and
 R^6 is $-X^6X^7R^{16}$, wherein X^6 is $-C(O)-$ or $-S(O)_2-$, X^7 is a bond, $-O-$ or
 $-NR^{17}-$, wherein R^{17} is hydrogen or (C_{1-6}) alkyl, and R^{16} is (i) (C_{1-6}) alkyl or
 halo-substituted (C_{1-6}) alkyl optionally substituted with $-OR^{11}$, $-SR^{11}$, $-S(O)R^{11}$,
 $-S(O)_2R^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, $-NR^{12}C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$,
 20 $-NR^{12}C(O)NR^{11}R^{12}$ or $-NR^{12}C(NR^{12})NR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined
 above, or (ii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-3}) alkyl,
 (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) polycycloaryl (C_{0-3}) alkyl or
 hetero (C_{8-12}) polycycloaryl (C_{0-3}) alkyl optionally substituted with 1 to 2 of $-R^{13}$,
 $-X^5OR^{13}$, $-X^5SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)OR^{13}$, $-X^5NR^{13}R^{14}$,
 25 $-X^5NR^{14}C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{14}C(O)NR^{13}R^{14}$ or
 $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein X^5 , R^{13} and R^{14} are as defined above; wherein any
 1 to 3 annular atoms of any aromatic ring with available valences comprising R^{16}
 optionally independently are substituted with halo, nitro, cyano, (C_{1-6}) alkyl,
 halo-substituted (C_{1-6}) alkyl, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{15}$,

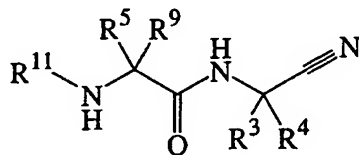
$-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{OR}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$ or

$-\text{X}^5\text{NR}^{15}\text{C}(\text{NR}^{15})\text{NR}^{15}\text{R}^{15}$, wherein X^5 and R^{15} are as defined above;

R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;

R^3 is hydrogen, (C_{1-10}) alkyl or as defined below; and

- 5 R^4 is (i) hydrogen, (ii) (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl optionally substituted with $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{11}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$ or $-\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{11}\text{R}^{12}$, wherein R^{11} and R^{12} are as defined above, or (iii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) polycycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) polycycloaryl (C_{0-3}) alkyl optionally substituted with $-\text{R}^{13}$, $-\text{X}^5\text{OR}^{13}$, $-\text{X}^5\text{SR}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{X}^5\text{NR}^{13}\text{R}^{14}$, $-\text{X}^5\text{NR}^{14}\text{C}(\text{O})\text{OR}^{13}$, $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$ or $-\text{NR}^{14}\text{C}(\text{NR}^{14})\text{NR}^{13}\text{R}^{14}$, wherein X^5 , R^{13} and R^{14} are as defined above or (iv) together with R^2 forms trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo, (C_{1-4}) alkyl or methylene or (v) together with R^3 forms ethylene, trimethylene or tetramethylene; wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R^4 optionally independently are substituted with halo, nitro, cyano, (C_{1-6}) alkyl, halo-substituted (C_{1-6}) alkyl, $-\text{OR}^{15}$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{OR}^{15}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$, $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{R}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{OR}^{15}$, $-\text{X}^5\text{NR}^{15}\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$ or $-\text{X}^5\text{NR}^{15}\text{C}(\text{NR}^{15})\text{NR}^{15}\text{R}^{15}$, wherein X^5 and R^{15} are as defined above; or an *N*-oxide derivative, prodrug derivative, individual isomer and mixtures of isomers; or a pharmaceutically acceptable salt thereof, but excluding compounds of the formula

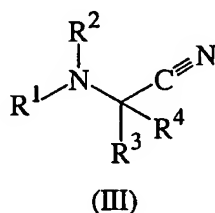


- in which R^3 and R^4 are each hydrogen or (C_{1-6}) alkyl, or together with the carbon atom to which they are both attached form (C_{3-5}) cycloalkylene; R^5 is hydrogen or (C_{1-6}) alkyl; R^9 is (C_{6-12}) aryl (C_{1-6}) alkyl, hetero (C_{5-12}) aryl (C_{1-6}) alkyl, (C_{4-5}) alkyl or cyclohexylmethyl; and R^{11} is

C(O)R¹⁸ wherein R¹⁸ is hetero(C₃₋₁₂)cycloalkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl.

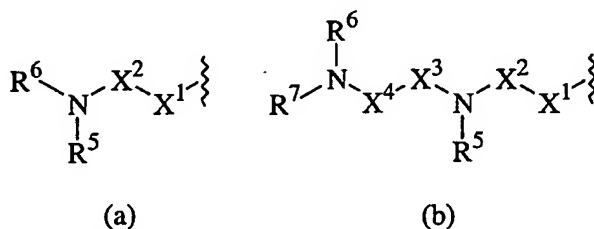
In another particular embodiment, the present invention relates to the use of a compound of Formula (III):

5



in which:

R¹ is a group of Formula (a) or (b):



wherein:

10 X¹ and X³ independently are -C(O)- or -S(O)₂-,
X² is -CR⁸R⁹-, -CH₂CR⁸R⁹- or -CR⁸R⁹CH₂- and X⁴ is -CHR¹⁰-,
-CH₂CHR¹⁰- or -CHR¹⁰CH₂-, wherein:

R⁸ is hydrogen or (C₁₋₆)alkyl,

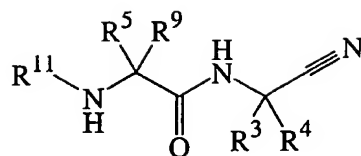
15 R⁹ is (i) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl optionally substituted with -OR¹¹, -SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)R¹¹, -C(O)OR¹¹, -NR¹¹R¹², -NR¹²C(O)OR¹¹, -C(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², -NR¹²C(O)NR¹¹R¹² or -NR¹²C(NR¹²)NR¹¹R¹², wherein R¹¹ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl and R¹² is hydrogen or
20 (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl,

hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl optionally substituted with -R¹³, -X⁵OR¹³, -X⁵SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -C(O)OR¹³, -X⁵NR¹³R¹⁴, -X⁵NR¹⁴C(O)OR¹³, -C(O)NR¹³R¹⁴, -S(O)₂NR¹³R¹⁴, -NR¹⁴C(O)NR¹³R¹⁴ or -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein X⁵ is a bond or methylene, R¹³ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl and R¹⁴ is hydrogen or (C₁₋₆)alkyl, or (iii) together with R⁵ when X² is -CHR⁹- forms trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with 1 to 2 of hydroxy, oxo, (C₁₋₄)alkyl or methylene; wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R⁹ are optionally independently substituted with halo, nitro, cyano, (C₁₋₆)alkyl, halo-substituted(C₁₋₆)alkyl, -OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)NR¹⁵R¹⁵, -S(O)₂NR¹⁵R¹⁵, -X⁵NR¹⁵R¹⁵, -X⁵NR¹⁵C(O)OR¹⁵, -X⁵NR¹⁵C(O)NR¹⁵R¹⁵ or -X⁵NR¹⁵C(NR¹⁵NR¹⁵R¹⁵), wherein X⁵ is as defined above and each R¹⁵ independently is hydrogen or (C₁₋₆)alkyl, and

R¹⁰ is hydrogen or (C₁₋₄)alkyl;

R⁵ and R⁷ are independently hydrogen, (C₁₋₆)alkyl or as defined above; and R⁶ is -X⁶X⁷R¹⁶, wherein X⁶ is -C(O)- or -S(O)₂-, X⁷ is a bond, -O- or -NR¹⁷-, wherein R¹⁷ is hydrogen or (C₁₋₆)alkyl, and R¹⁶ is (i) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl optionally substituted with -OR¹¹, -SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)R¹¹, -C(O)OR¹¹, -NR¹¹R¹², -NR¹²C(O)OR¹¹, -C(O)NR¹¹R¹², -NR¹²C(O)NR¹¹R¹² or -NR¹²C(NR¹²)NR¹¹R¹², wherein R¹¹ and R¹² are as defined above, or (ii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl optionally substituted with 1 to 2 of -R¹³, -X⁵OR¹³, -X⁵SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)OR¹³, -X⁵NR¹³R¹⁴,

- X⁵NR¹⁴C(O)OR¹³, -C(O)NR¹³R¹⁴, -NR¹⁴C(O)NR¹³R¹⁴ or
 -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein X⁵, R¹³ and R¹⁴ are as defined above; wherein any
 1 to 3 annular atoms of any aromatic ring with available valences comprising R¹⁶
 optionally independently are substituted with halo, nitro, cyano, (C₁₋₆)alkyl,
 5 halo-substituted(C₁₋₆)alkyl, -OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)NR¹⁵R¹⁵,
 -S(O)₂NR¹⁵R¹⁵, -X⁵NR¹⁵R¹⁵, -X⁵NR¹⁵C(O)OR¹⁵, -X⁵NR¹⁵C(O)NR¹⁵R¹⁵ or
 -X⁵NR¹⁵C(NR¹⁵)NR¹⁵R¹⁵, wherein X⁵ and R¹⁵ are as defined above;
 R² is hydrogen or (C₁₋₆)alkyl or as defined below;
 R³ is hydrogen, (C₁₋₁₀)alkyl or as defined below; and
 10 R⁴ is (i) hydrogen, (ii) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl optionally substituted
 with -OR¹¹, -SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -C(O)R¹¹, -C(O)OR¹¹, -NR¹¹R¹²,
 -NR¹²C(O)OR¹¹, -C(O)NR¹¹R¹², -NR¹²C(O)NR¹¹R¹² or -NR¹²C(NR¹²)NR¹¹R¹², wherein
 R¹¹ and R¹² are as defined above, or (iii) (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl,
 15 (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl optionally substituted
 with -R¹³, -X⁵OR¹³, -X⁵SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)OR¹³, -X⁵NR¹³R¹⁴,
 -X⁵NR¹⁴C(O)OR¹³, -C(O)NR¹³R¹⁴, -NR¹⁴C(O)NR¹³R¹⁴ or -NR¹⁴C(NR¹⁴)NR¹³R¹⁴,
 wherein X⁵, R¹³ and R¹⁴ are as defined above or (iv) together with R² forms trimethylene,
 tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo, (C₁₋₆)alkyl or methylene or (v) together with R³ forms ethylene, trimethylene or tetramethylene;
 20 wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R⁴
 optionally independently are substituted with halo, nitro, cyano, (C₁₋₆)alkyl,
 halo-substituted(C₁₋₆)alkyl, -OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)NR¹⁵R¹⁵,
 -S(O)₂NR¹⁵R¹⁵, -X⁵NR¹⁵R¹⁵, -X⁵NR¹⁵C(O)OR¹⁵, -X⁵NR¹⁵C(O)NR¹⁵R¹⁵ or
 25 -X⁵NR¹⁵C(NR¹⁵)NR¹⁵R¹⁵, wherein X⁵ and R¹⁵ are as defined above; or an *N*-oxide
 derivative, prodrug derivative, individual isomer and mixtures of isomers; or a
 pharmaceutically acceptable salt thereof, but excluding compounds of the formula



in which R^3 and R^4 are each hydrogen or (C_{1-6}) alkyl, or together with the carbon atom to which they are both attached form (C_{3-8}) cycloalkylene; R^5 is hydrogen or (C_{1-6}) alkyl; R^9 is (C_{6-12}) aryl (C_{1-6}) alkyl, hetero (C_{5-12}) aryl (C_{1-6}) alkyl, (C_{4-5}) alkyl or cyclohexylmethyl; and R^{11} is

5 $C(O)R^{18}$ wherein R^{18} is hetero (C_{3-12}) cycloalkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl, in the manufacture of a medicament for treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

10 Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the meanings given this Section:

“Alicyclic” means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

15 “Aliphatic” means a moiety characterized by straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

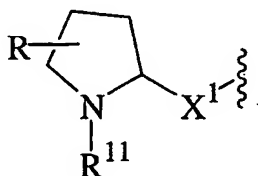
“Alkyl” indicated alone means a straight or branched, saturated or unsaturated aliphatic radical having the number of carbon atoms indicated (e.g., (C_{1-6}) alkyl includes

20 methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl indicated as part of a larger radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when 0 atoms are indicated means a bond (e.g., (C_{0-3}) alkyl of

(C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl means a bond, methylene, ethylene, trimethylene, 1-methylethylene, or the like).

“Alkylene”, unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g.

- 5 (C₁₋₆)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), 2-methyltrimethylene (-CH₂CH(CH₃)CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-), 2-butenylene (-CH₂CH=CHCH₂-), 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-) and the like). For example, the instance wherein R⁵ is hydrogen and R⁹ taken together with R⁷ forms optionally
- 10 substituted trimethylene is illustrated by the following:



in which R is an optional hydroxy or oxo group and X¹ and R¹¹ are as defined in the Summary of the Invention.

- “Alkylidene” means a straight or branched saturated or unsaturated, aliphatic, divalent
- 15 radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkylidene includes methylene (CH₂), ethylidene (CHCH₃), isopropylidene (C(CH₃)₂), propylidene (CHCH₂CH₃), allylidene (CHCH=CH₂), and the like).

- “Amino” means the radical -NH₂. Unless indicated otherwise, the compounds of the invention containing amino moieties include protected derivatives thereof. Suitable protecting
- 20 groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

“Animal” includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, etc.) and non-mammals (e.g., birds, etc.).

"Aryl" means a monocyclic or bicyclic ring assembly (fused or linked by a single bond) containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly. For example, (C₆₋₁₂)aryl includes phenyl, naphthyl and biphenyl.

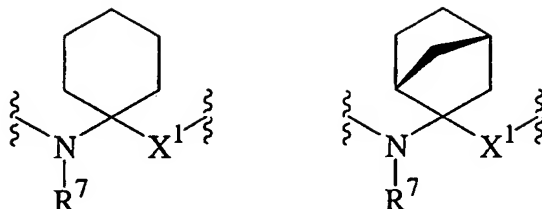
5 "Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp² hybridized and the total number of pi electrons is equal to 4n + 2.

"Carbamoyl" means the radical -C(O)NH₂. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include protected derivatives
10 thereof. Suitable protecting groups for carbamoyl moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

"Carboxy" means the radical -C(O)OH. Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable
15 protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic ring, bicyclic ring assembly (directly linked by a single bond or fused) or bridged polycyclic ring assembly containing the number of annular carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C₃₋₁₂)cycloalkyl includes cyclopropyl,
20 cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclohexyl, cyclopentylcyclohexyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthalenyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, etc.).

"Cycloalkylene" means a saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of annular carbon atoms indicated,
25 and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the instance wherein R⁹ and R⁵ together with the carbon atom to which both R⁹ and R⁵ are attached form (C₃₋₈)cycloalkylene" includes, but is not limited to, the following:



in which X¹ and R⁷ are as defined in the Summary of the Invention.

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or
 5 veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Guanidino" means the radical -NHC(NH)NH₂. Unless indicated otherwise, the compounds of the invention containing guanidino moieties include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

10 "Halo" means fluoro, chloro, bromo or iodo.

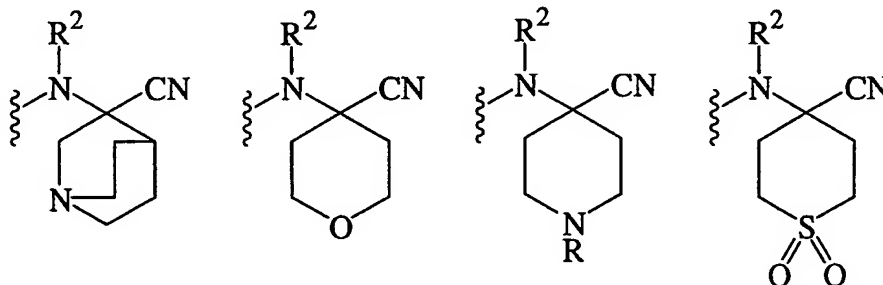
"Halo-substituted alkyl", as a group or part of a group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C₁₋₃)alkyl includes chloromethyl, dicloromethyl, difluoromethyl,
 15 trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N-, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group, and each
 20 ring contained therein is comprised of 5 to 6 ring member atoms. For example, hetero(C₅₋₁₂)aryl as used in this Application includes benzofuryl, benzooxazolyl, benzothiazolyl, [2,4']bipyridinylyl, carbazolyl, carbolinylyl, chromenyl, cinnolinyl, furazanyl, furyl, imidazolyl, indazolyl, indolyl, indolizinylyl, isobenzofuryl, isochromenyl, isooxazolyl, isoquinolyl, isothiazolyl, naphthyridinylyl, oxazolyl, perimidinylyl, 2-phenylpyridyl, phthalazinyl, pteridinylyl,
 25 purinyl, pyrazinyl, pyradazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolizinylyl, pyrrolidinyl, pyrrolyl, pyranlyl, quinazolinyl, quinolizinylyl, quinolyl, quinoxalinylyl, tetrazolyl, thiazolyl,

4-thiazol-4-ylphenyl, thienyl, xanthenyl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like.

“Heterocycloalkyl” means cycloalkyl, as defined herein, provided that one or more of the ring member carbon atoms indicated is replaced by heteroatom moiety selected from -N-, -NR-, -O-, -S- or -S(O)₂, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g. the term hetero(C₅₋₁₂)cycloalkyl includes [1,4']bipiperidinyl, dihydrooxazolyl, morpholinyl, 1-morpholin-4-ylpiperidinyl, piperazinyl, piperidyl, pirazolidinyl, pirazolinyl, pyrrolinyl, pyrrolidinyl, quinuclidinyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. For example, a compound of Formula I wherein R¹ is piperidin-4-ylcarbonyl may exist as either the unprotected or a protected derivative, e.g. wherein R¹ is 1-*tert*-butoxycarbonylpiperidin-4-ylcarbonyl, and both the unprotected and protected derivatives fall within the scope of the invention.

“Heterocycloalkylene” means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N-, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen or (C₁₋₆)alkyl. For example, the instance wherein R³ and R⁴ together with the carbon atom to which both R³ and R⁴ are attached form hetero(C₃₋₈)cycloalkylene” includes, but is not limited to, the following:



in which R is hydrogen, (C₁₋₆)alkyl or a protecting group and R² is as defined in the Summary of the Invention.

"Heteropolycycloaryl" means polycycloaryl, as defined herein, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety selected from -N-, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group, and any carbocyclic ketone, thioketone or iminoketone derivative thereof

- 5 (e.g., hetero(C₈₋₁₂)polycycloaryl includes 3,4-dihydro-2*H*-quinolinyl, 5,6,7,8-tetrahydroquinolinyl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, morpholinylpyridyl, piperidinylphenyl, 1,2,3,4,5,6-hexahydro-[2,2']bipyridinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, etc.).

- "Heteroatom moiety" includes -N-, -NR-, -O-, -S- or -S(O)₂-, wherein R is
10 hydrogen, (C₁₋₆)alkyl or a protecting group.

- "Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like. For example, a compound of Formula I wherein the R⁹ contains a hydroxy moiety exist as either the unprotected or a
15 protected derivative, e.g., wherein R⁹ is benzyloxybenzyl, and both the unprotected and protected derivatives fall within the scope of the invention.

"Iminoketone derivative" means a derivative containing the moiety -C(NR)-, wherein R is hydrogen or (C₁₋₆)alkyl.

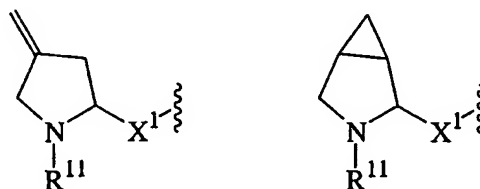
- "Isomers" mean compounds of Formula I having identical molecular formulae but
20 differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereo isomers". Stereo isomers that are not mirror images of one another are termed "diastereomers" and stereo isomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical
25 substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{*n*-1} enantiomeric pairs, where *n* is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one

chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and

5 Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereo isomers are well known in the art (e.g., see "Advanced Organic Chemistry", 3rd edition, March, Jerry, John Wiley & Sons, New York, 1985). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereo isomers. Thus, for
10 example, the name 1-(1-cyano-1-methylethylcarbamoyl)-3-methylbutylcarbamate is meant to include 1*S*-(1-cyano-1-methylethylcarbamoyl)-3-methylbutylcarbamate and 1*R*-(1-cyano-1-methylethylcarbamoyl)-3-methylbutylcarbamate and any mixture, racemic or otherwise, thereof.

"Ketone derivative" means a derivative containing the moiety -C(O)-.

15 "Methylene" means the divalent radical -CH₂- or CH₂, wherein its free valances can be attached to different atoms or the same atom. For example, the instance wherein R⁹ together with R⁷ forms trimethylene substituted methylene includes the following:



in which X¹ and R¹¹ are as defined in the Summary of the invention, and may be referred to as
20 2,2-methylene and 1,2-methylene, respectively.

"Nitro" means the radical -NO₂.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase
25 "any 1 to 3 annular atoms of any aromatic ring with available valences comprising R⁶ optionally independently is substituted" means that the aromatic ring referred to may or may

not be substituted in order to fall within the scope of the invention.

"N-oxide derivatives" means a derivatives of compound of Formula I in which nitrogens are in an oxidized state (i.e., O-N) and which possess the desired pharmacological activity.

5 "Oxo" means the radical O.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

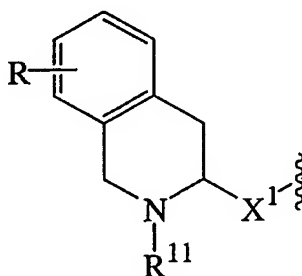
"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor
10 otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids
15 such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, maleic acid, methanesulfonic acid,
20 ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid,
25 hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, ammonium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable

organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Phenylene-1,2-dimethylene" means the divalent radical $-\text{CH}_2\text{C}_6\text{H}_4\text{CH}_2-$, wherein the methylene moieties are attached at the 1- and 2-positions of the phenylene moiety. For example, a group of Formula (a), wherein R^9 together with R^7 form optionally substituted phenylene-1,2-dimethylene is illustrated by the following formula:



in which R is an optional hydroxy or (C_{1-4}) alkyl group and X^1 and R^{11} are as defined in the Summary of the Invention.

"Polycycloaryl" means a bicyclic ring assembly (directly linked by a single bond or fused) containing the number of ring member carbon atoms indicated, wherein at least one, but not all, of the fused rings comprising the radical is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{9-12}) polycycloaryl includes indanyl, indenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2-dihydronaphthalenyl, cyclohexylphenyl, phenylcyclohexyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthalenyl, and the like).

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula (I). For example an ester of a compound of Formula (I) containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of Formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of Formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates,

methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. Suitable esters of compounds of Formula (I) containing a carboxy group, are for example those described by F.J. Leinweber, *Drug Metab. Res.*, 1987, 18, page 379. An especially useful class of esters of compounds of Formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et. al., *J. Med. Chem.*, 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active cysteine protease inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

"Treatment" or "treating" means any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or

symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

"Ureido" means the radical -NHC(O)NH_2 . Unless indicated otherwise, the compounds of the invention containing ureido moieties include protected derivatives thereof. Suitable protecting groups for ureido moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like. For example, a compound of Formula I wherein the R^9 contains an ureido moiety may exist as either the unprotected or a protected derivative and the like, and both the unprotected and protected derivatives fall within the scope of the invention.

Presently Preferred Embodiments:

While the broadest definition of the invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred. Preferred are compounds of Formula I in which:

R^1 represents a group of Formula (a) wherein within Formula (a):

X^1 is -C(O)- ;

R^5 represents hydrogen or (C_{1-6}) alkyl, preferably hydrogen;

R^7 represents hydrogen or methyl, preferably hydrogen,

R^9 represents (i) (C_{1-6}) alkyl optionally substituted with -OR^{14} , -SR^{14} , -S(O)R^{14} , $\text{-S(O)}_2\text{R}^{14}$, -C(O)R^{14} , -C(O)OR^{14} , -OC(O)R^{14} , $\text{-NR}^{14}\text{R}^{15}$, $\text{-NR}^{15}\text{C(O)R}^{14}$, $\text{-NR}^{15}\text{C(O)OR}^{14}$, $\text{-C(O)NR}^{14}\text{R}^{15}$, $\text{-S(O)}_2\text{NR}^{14}\text{R}^{15}$, $\text{-NR}^{15}\text{C(O)NR}^{14}\text{R}^{15}$ or $\text{-NR}^{15}\text{C(NR}^{15})\text{NR}^{14}\text{R}^{15}$, wherein R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) polycycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) polycycloaryl (C_{0-6}) alkyl and R^{15} is hydrogen or (C_{1-6}) alkyl, and wherein within R^{14} said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R^{16} , $\text{-X}^3\text{OR}^{16}$, $\text{-X}^3\text{SR}^{16}$, $\text{-X}^3\text{S(O)R}^{16}$, $\text{-X}^3\text{S(O)}_2\text{R}^{16}$, $\text{-X}^3\text{C(O)R}^{16}$, $\text{-X}^3\text{C(O)OR}^{16}$, $\text{-X}^3\text{OC(O)R}^{16}$, $\text{-X}^3\text{NR}^{16}\text{R}^{17}$, $\text{-X}^3\text{NR}^{17}\text{C(O)R}^{16}$, $\text{-X}^3\text{NR}^{17}\text{C(O)OR}^{16}$, $\text{-X}^3\text{C(O)NR}^{16}\text{R}^{17}$, $\text{-X}^3\text{S(O)}_2\text{NR}^{16}\text{R}^{17}$, $\text{-X}^3\text{NR}^{17}\text{C(O)NR}^{16}\text{R}^{17}$ or

-X³NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X³ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)polycycloaryl(C₀₋₆)alkyl, or (ii) a group selected from

5 (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₀)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X³OR¹⁶, -X³SR¹⁶, -X³S(O)R¹⁶, -X³S(O)₂R¹⁶,

10 -X³C(O)R¹⁶, -X³C(O)OR¹⁶, -X³OC(O)R¹⁶, -X³NR¹⁶R¹⁷, -X³NR¹⁷C(O)R¹⁶, -X³NR¹⁷C(O)OR¹⁶, -X³C(O)NR¹⁶R¹⁷, -X³S(O)₂NR¹⁶R¹⁷, -X³NR¹⁷C(O)NR¹⁶R¹⁷ or -X³NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X³, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo,

15 halo-substituted (C₁₋₄)alkyl, nitro, -X³NR¹²R¹², -X³NR¹²C(O)OR¹², -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR³)OR¹², -X³OP(O)(OR³)OR¹², -X³OC(O)R¹³, -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³ and -X³C(O)R¹³, wherein X³ is as defined above, R¹² at each occurrence

20 independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and

R¹¹ represents -X⁴X⁵R¹⁸, wherein X⁴ is -C(O)- or -S(O)₂-, X⁵ is a bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is (i) (C₁₋₁₀)alkyl or

(ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,

25 (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by -X⁹OR²⁴, -X⁹C(O)R²⁴, -X⁹C(O)OR²⁴, -X⁹C(O)NR²⁴R²⁵, -X⁹NR²⁴R²⁵, -X⁹NR²⁵C(O)R²⁴, -X⁹NR²⁵C(O)OR²⁴, -X⁹NR²⁵C(O)NR²⁴R²⁵ or

-X⁹NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁹ is a bond or (C₁₋₆)alkylene, R²⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ is hydrogen or (C₁₋₆)alkyl, wherein within R¹¹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5
 5 substituents independently selected from (C₁₋₆)alkyl, halo, halo-substituted (C₁₋₄)alkyl, -OR¹², -X³SR¹², -C(O)OR¹² and -X³NR¹²C(O)OR¹², wherein X³ is a bond or (C₁₋₆)alkylene and R¹⁴ is hydrogen or (C₁₋₆)alkyl.

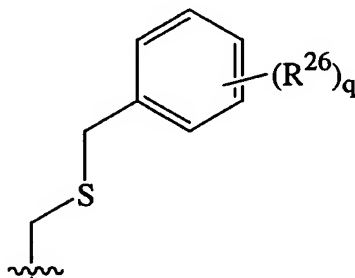
Within Formula (a), R¹¹ particularly represents -X⁴X⁵R¹⁸, wherein X⁴ is -C(O)-, X⁵ is a bond and R¹⁸ is (i) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl or (ii) phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said phenyl or heteroaryl is substituted by -X⁹OR²⁴, -X⁹C(O)R²⁴, -X⁹C(O)OR²⁴, -X⁹C(O)NR²⁴R²⁵, -X⁹NR²⁴R²⁵, -X⁹NR²⁵C(O)R²⁴, -X⁹NR²⁵C(O)OR²⁴, -X⁹NR²⁵C(O)NR²⁴R²⁵ or -X⁹NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁹ is a bond or (C₁₋₆)alkylene, R²⁴ is phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ is
 15 hydrogen or (C₁₋₆)alkyl, wherein within R¹¹ any aromatic ring system present may be substituted further by 1 to 5 substituents independently selected from (C₁₋₆)alkyl, halo, halo-substituted (C₁₋₄)alkyl, -OR¹², -X³SR¹², -C(O)OR¹² and -X³NR¹²C(O)OR¹² wherein X³ is a bond or (C₁₋₆)alkylene and R¹² is hydrogen or (C₁₋₆)alkyl.

Within Formula (a), R¹¹ more particularly represents benzoyl, furylcarbonyl, phenyloxybenzoyl, pyridylthienylcarbonyl, benzoylbenzoyl, thienylcarbonyl, morpholinylcarbonyl, phenyluriedobenzoyl, cyclohexenylcarbonyl or piperazinylcarbonyl, wherein within R¹¹ any aromatic ring system present may be substituted further by 1 to 2 substituents independently selected from (C₁₋₆)alkyl, *tert*-butoxycarbonylamino, *tert*-butoxycarbonylaminomethyl, bromo, chloro, ethoxy, fluoro, hydroxy, methoxy and
 25 methylsulfanyl.

Within Formula (a), R⁹ particularly represents (i) (C₁₋₆)alkyl optionally substituted with -OR¹⁴ or -SR¹⁴, wherein R¹⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl, biphenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, or (ii) a group selected from (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl, biphenyl(C₀₋₆)alkyl or

- hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl; wherein within R⁹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X³NR¹²R¹², -X³NR¹²C(O)OR¹², -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR³)OR¹², -X³OP(O)(OR³)OR¹², -X³OC(O)R¹³, -X³OC(O)R¹³, -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³ and -X³C(O)R¹³, wherein X³ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl.
- 10 Within Formula (a), R⁹ more particularly represents cyclohexylmethyl, wherein said cyclohexyl may be substituted by 1 to 5 radicals independently selected from (C₁₋₄)alkyl, (C₁₋₆)alkylidene or -X³OC(O)R¹³, or phenylmethylsulfanylmethyl or phenylsulfanylethyl, wherein said phenyl may be substituted by 1 to 5 radicals independently selected from (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -OR¹², -SR¹² and -C(O)OR¹²,
- 15 wherein R¹² is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl.

Within Formula (a), R⁹ more particularly presents a group having the following formula:



- 20 in which q is 0 to 5 and R²⁶ at each occurrence is independently selected from (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -OR¹², -SR¹² and -C(O)OR¹², wherein R¹² is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₆)alkyl or halo-substituted

(C₁₋₃)alkyl.

Within Formula (a), R⁹ preferably represents benzylsulfanylmethyl, 2-bromobenzylsulfanylmethyl, 2-chlorobenzylsulfanyl, 2-(2-chlorophenylsulfanyl)ethyl, cyclohexyl, 4-ethylidenecyclohexyl, 2-iodobenzylsulfanylmethyl, 2-methylbenzylsulfanylmethyl, 3-methyl-3-trifluorocarbonyloxycyclohexylmethyl, 4-methylenecyclohexylmethyl or 2-nitrobenzylsulfanylmethyl.

R² preferably represents hydrogen;

R³ preferably is hydrogen or (C₁₋₄)alkyl, typically hydrogen, or taken with R⁴ together with the carbon atom to which both R³ and R⁴ are attached form (C₃₋₈)cycloalkylene (e.g. cyclopropylene or cyclohexylene).

R⁴ preferably is hydrogen or taken with R³ together with the carbon atom to which both R³ and R⁴ are attached form (C₃₋₈)cycloalkylene (e.g. cyclopropylene or cyclohexylene).

Compounds of Formula II specifically include those in which R⁹ represents (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴ or -X⁴NR¹⁴R¹⁵, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ is (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl and R¹⁵ is hydrogen or (C₁₋₆)alkyl, and wherein within R⁹ said aryl or heteroaryl ring optionally is substituted by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴OR¹², -X⁴C(O)R¹², -X⁴SR¹², wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl.

Compounds of Formula II particularly include those in which R⁹ represents benzyl, benzyloxymethyl, benzylsulfanylethyl, benzylsulfanylmethyl, benzylsulfanylmethyl, indolylmethyl, naphthylmethyl, phenethyl, phenoxyethyl, phenylamino, pyridylmethyl, pyridylsulfanylethyl, phenylsulfanylethyl, thiazolyl or thienyl, wherein within R⁹ the aromatic ring may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴OR¹², -X⁴C(O)R¹², -X⁴SR¹², wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl.

- Compounds of Formula II more particularly include those in which R⁹ represents
- 4-aminobenzyl, benzyl, benzyloxymethyl, 2-benzylsulfanylethyl, benzylsulfanylmethyl,
 2-bromobenzylsulfanylmethyl, 4-*tert*-butylbenzylsulfanylmethyl, 2-chlorobenzyl,
 4-chlorobenzyl, 2-chlorobenzylsulfanylmethyl, 4-chlorobenzylsulfanylmethyl,
 5 2-(2-chlorophenylsulfanyl)ethyl, 4-cyanobenzyl, 3,4-dichlorobenzylsulfanylmethyl,
 1,6-dichlorobenzyl, 3,5-dimethylbenzylsulfanylmethyl, 2-fluorobenzyl, 4-fluorobenzyl,
 2-fluorobenzylsulfanylmethyl, 1-formylindol-3-ylmethyl, indol-3-ylmethyl,
 2-iodobenzylsulfanylmethyl, 2-methylbenzylsulfanylmethyl, 3-methylbenzylsulfanylmethyl,
 3-methylbenzylsulfanylmethyl, 4-methylbenzylsulfanylmethyl, 2-(2-methylphenylsulfanyl)ethyl,
 10 4-methoxybenzyl, 4-methoxybenzylsulfanylmethyl, 4-methoxybenzylsulfanylmethyl,
 naphth-2-ylmethyl, naphth-2-ylmethylsulfanylmethyl, 3-nitrobenzyl,
 1-nitrobenzylsulfanylmethyl, 2-nitrobenzylsulfanylmethyl, 3-nitrobenzylsulfanylmethyl,
 4-nitrobenzylsulfanylmethyl, 4-nitrobenzyl, pentafluorobenzylsulfanylmethyl, phenylamino,
 phenethyl, phenethyloxy, 2-phenoxyethyl, 2-phenoxyethyl 2-phenylsulfanylethyl,
 15 pyrid-4-ylmethyl, pyrid-2-ylmethylsulfanylmethyl, pyrid-3-ylmethylsulfanylmethyl,
 pyrid-4-ylmethylsulfanylmethyl, 2-pyrid-2-ylsulfanylethyl, 2-pyrid-4-ylsulfanylethyl,
 thiazol-5-yl, thien-2-ylmethyl, 4-trifluoromethylbenzylsulfanylmethyl,
 3-trifluoromethylbenzylsulfanylmethyl, 3-trifluoromethoxybenzylsulfanylmethyl,
 4-trifluoromethoxybenzylsulfanylmethyl or 4-trifluorosulfanylbenzylsulfanylmethyl,
 20 Reference to the preferred embodiments set forth above is meant to include all
 combinations of particular and preferred groups.

Further preferred are compounds of Formula I selected from a group consisting of:

- N*-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)-4-hydroxybenzamide;
N-[2-(2-bromobenzylsulfanyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
 25 *N*-[1*R*-cyanomethylcarbamoyl-2-(2-iodobenzylsulfanyl)ethyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(2-cyanobenzylsulfanyl)ethyl]morpholine-
 4-carboxamide;
N-[3-(2-chlorophenylsulfanyl)-1*R*-cyanomethylcarbamoylpropyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfanyl)ethyl]morpholine-

4-carboxamide

N-[1*R*-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]morpholine-

4-carboxamide; and

N-[1*R*-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]benzamide.

5 Pharmacology and Utility:

The compounds of the invention are cysteine protease inhibitors, in particular the compounds of the invention inhibit the activity of cathepsins B, L, K and/or S and, as such, are useful for treating diseases in which cathepsin B, L, K and/or S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the

10 invention are useful in treating tumor invasion and metastasis, in particular as anti-angiogenic agents, rheumatoid arthritis, osteo arthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders. Furthermore, the compounds of the invention are useful in treating bone resorption disorders, e.g., osteoporosis. The compounds of the invention also are useful in treating autoimmune disorders, including, but not

15 limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotatus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders, including, but not limited to asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts.

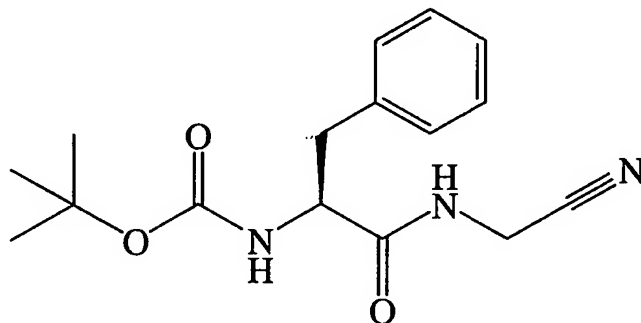
The cysteine protease inhibitory activities of the compounds of the invention can be

20 determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease induced hydrolysis of a peptide based substrate. Details of assays for measuring protease inhibitory activity are set forth in Examples 10, 11, 12 and 13, *infra*.

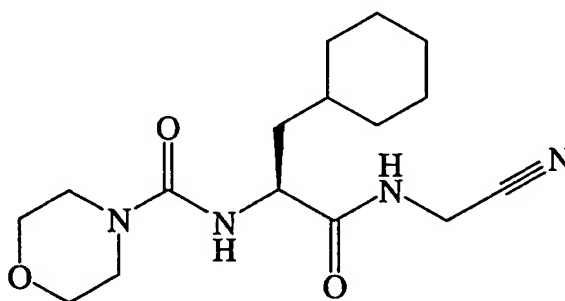
25 Nomenclature:

The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the

characteristic groups have decreasing priority for citation as the principle group as follows:
acids, esters, amides and amidines. For example, a compound of Formula I in which R¹ is a
group of Formula (a), wherein X¹ is carbonyl, R⁵ and R⁷ are each hydrogen, R⁹ is benzyl and
R¹¹ is *tert*-butoxycarbonyl and R², R³ and R⁴ are each hydrogen; that is, a compound having
5 the following structure:



is named *tert*-butyl 1*S*-cyanomethylcarbamoyl-2-phenylethylcarbamate and a compound of
Formula I in which R¹ is a group of Formula (a), wherein X¹ is carbonyl, R⁵ and R⁷ are each
hydrogen, R⁹ is cyclohexylmethyl and R¹¹ is morpholin-4-ylcarbonyl and R², R³ and R⁴ are
10 each hydrogen; that is, a compound having the following structure:



is named *N*-(1*S*-Cyanomethylcarbamoyl-2-cyclohexylethyl)morpholine-4-carboxamide.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective
15 amounts via any of the usual and acceptable modes known in the art, either singly or in
combination with another therapeutic agent. A therapeutically effective amount may vary

widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from 0.1 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to 10 milligram per kilogram body weight (mg/kg) per day, typically 1 $\mu\text{g/kg/day}$ to 1 mg/kg/day . Therefore, a therapeutically effective amount for a 80 kg human patient may range from 10 $\mu\text{g/day}$ to 100 mg/day , typically 0.1 mg/day to 10 mg/day . In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

10 The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in
15 general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

20 Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean
25 oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition

of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 15.

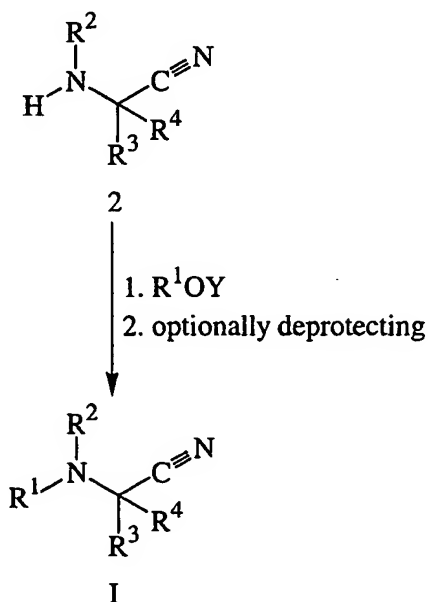
Chemistry:

Processes for Making Compounds of Formula I:

Compounds of Formula I can be prepared by proceeding as in the following

10 Scheme 1:

Scheme 1



in which Y is hydrogen or an activating group (e.g., 2,5-dioxopyrrolidin-1-yl (NBS), and the like) and each R¹, R², R³ and R⁴ are as defined in the Summary of the Invention.

15 Compounds of Formula I can be prepared by reacting a compound of Formula 2, or

a protected derivative thereof, with a compound of the formula R^1OY , or a protected derivative thereof, and then optionally deprotecting. The reaction is carried out in the presence of a suitable acylation catalyst (e.g., triethylamine) and in a suitable solvent (e.g., acetonitrile, *N,N*-dimethylformamide (DMF), methylene chloride, or any suitable combination thereof) at 10 to 30°C, preferably at about 25°C, and requires 24 to 30 hours to complete. When Y is hydrogen the reaction can be effected in the presence of a suitable coupling agent (e.g., benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and base (e.g., *N,N*-diisopropylethylamine, triethylamine, or the like) and requires 2 to 15 hours to complete. Alternatively, when Y is hydrogen the reaction can be carried out by treating the compound of formula R^1OH with *N*-methylmorpholine and isobutyl chloroformate in a suitable solvent (e.g., THF, or the like) at between 0 and 5°C for 30 minutes to an hour and then introducing the compound of Formula 2 to the reaction mixture and allowing the reaction to proceed for 12 to 15 hours.

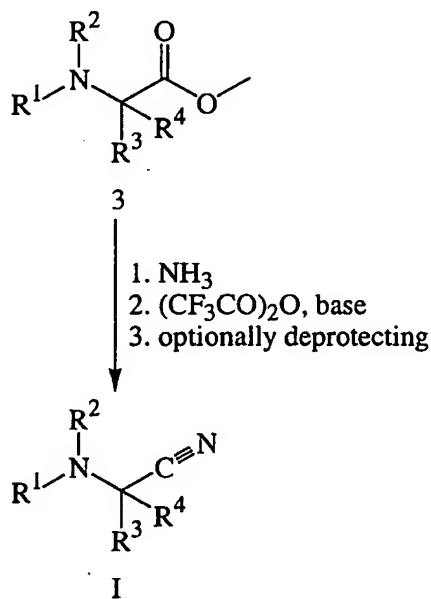
Deprotection can be effected by any means which removes the protecting group and gives the desired product in reasonable yield. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981. A detailed description of the preparation of a compound of Formula I according to Scheme 1 is set forth in Examples 4, 5, 6 and 8, *infra*.

Alternatively, compounds of Formula I can be prepared by reacting a compound of Formula 2 with a compound of the formula R^1-SS , wherein SS is a suitable solid support (e.g., thiophenol resin, or the like). The reaction can be carried out in the presence of a suitable acylation catalyst (e.g., 4-dimethylaminopyridine, or the like) and in a suitable solvent (e.g., dry pyrimidine, or the like) and requires 60 to 70 hours to complete.

Compounds of Formula I can be prepared by proceeding as in the following reaction

Scheme 2:

Scheme 2



5 in which each R¹, R², R³ and R⁴ are as defined in the Summary of the Invention.

Compounds of Formula I can be prepared by treating a compound of Formula 3, or a protected derivative thereof, with ammonia to provide a corresponding amide, then reacting the amide with a suitable dehydrating agent (e.g., trifluoroacetic anhydride, cyanuric chloride, thionyl chloride, phosphonyl chloride, and the like) and optionally deprotecting. The reaction
10 with the ammonia is carried out in a suitable solvent (e.g., methanol) at between 0 and 5°C and requires 6 to 10 days to complete. The reaction with the dehydrating agent is carried out in the presence of a suitable base (e.g., triethylamine) and in a suitable solvent (e.g., tetrahydrofuran (THF), and the like) at between 0 and 50°C and requires 1 to 2 hours to complete. A detailed description of the preparation of a compound of Formula I according to
15 Scheme 2 is set forth in Examples 7 and 8, *infra*.

Additional Processes for Preparing Compounds of Formula I:

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application. Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, etc.). A compound of Formula I in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as methylene chloride) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, etc.) in a suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, etc.) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods

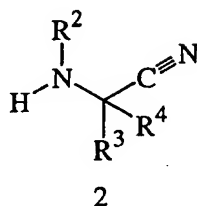
known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*. 4:1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, etc.).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Compounds of Formula I can be prepared as their individual stereo isomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereo isomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

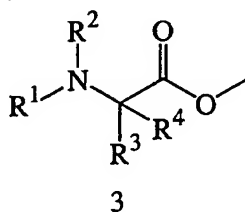
In summary, an aspect of the invention is a process for preparing a compound of Formula I, which process comprises:

(A) reacting a compound of Formula 2:



5 or a protected derivative thereof with a compound of the formula R^1OY , or a protected derivative thereof, in which Y is hydrogen or an activating group and each R^1 , R^2 , R^3 and R^4 are as defined in the Summary of the Invention; or

(B) reacting a compound of Formula 3:



10 with ammonia to provide a corresponding amide and then reacting the amide with trifluoroacetic anhydride, in which each R^1 , R^2 , R^3 and R^4 are as defined in the Summary of the Invention

- (C) optionally deprotecting a protected derivative of a compound of Formula I to provide a corresponding unprotected derivative;
- 15 (D) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;
- (E) optionally converting a salt form of a compound of Formula I to non-salt form;
- (F) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;
- 20 (G) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized

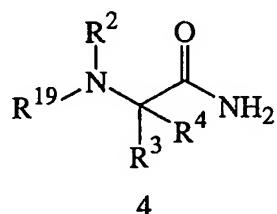
form;

(H) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

- (I) optionally converting a prodrug derivative of a compound of Formula I to its
5 non-derivatized form.

Processes for Preparing Intermediates:

Compounds of Formula 2 can be prepared by reacting a compound of Formula 4:

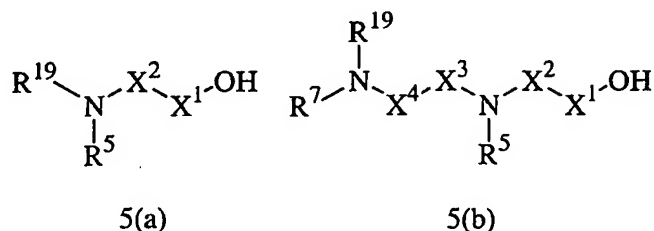


- in which R¹⁹ is an amino protecting group and each R², R³ and R⁴ are as defined in the
10 Summary of the Invention, with thionyl chloride and then deprotecting. The reaction with the thionyl chloride is carried out in the presence of a suitable base (e.g., triethylamine) and in a suitable solvent (e.g., DMF) at between 0 and 5 °C and requires 30 minutes to an hour to complete. Alternatively, compounds of Formula 2 can be prepared by reacting a compound of Formula 4 with trifluoroacetic anhydride. The deprotection can be effected by any means
15 which removes the protecting group and gives the desired product in reasonable yield. A detailed description of the preparation of a compound of Formula 2 according to above-described procedure is set forth in Example 1, *infra*.

- Compounds of Formula 4 can be prepared by treating a corresponding alkanoyl halide with ammonia. The treatment is carried out in a suitable solvent (e.g., dichloromethane,
20 5% aqueous sodium carbonate, and the like, or any suitable combination thereof) at 10 to 30 °C and requires 30 minutes to an hour to complete. The alkanoyl halide intermediates can be prepared from the corresponding alkanic acid by treating with thionyl chloride in a suitable solvent (e.g., dichloromethane) under nitrogen for 30 minutes to an hour. A detailed description of the preparation of a compound of Formula 2 according to the above-described

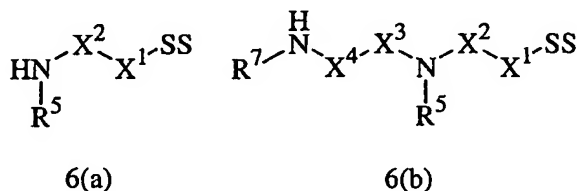
procedures is set forth in Example 1, *infra*.

Compounds of the formula R^1 -SS can be prepared by reacting a compound of Formula 5(a) or 5(b):



- 5 in which R^{19} is an amino protecting group (e.g., tert-butoxycarbonyl, fluoren-9-ylmethoxycarbonyl, or the like) and each X^1 , X^2 , X^3 , R^5 and R^7 are as defined for Formula I in the Summary of the Invention, with a suitable solid support resin (e.g., Wang (4-benzyloxybenzyl alcohol) resin, thiophenol resin, or the like), deprotecting to provide, respectively, a compound of Formula 6(a) or 6(b):

10



in which SS is a solid support and then reacting the compound of Formula 6(a) or 6(b) with a compound of the formula R^6OH (e.g., benzoic acid, indole-5-carboxylic acid, methanesulfonic acid, or the like).

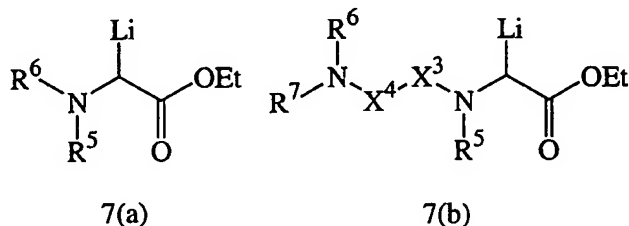
- The reaction between the compound of Formula 5(a) or 5(b) and the resin is carried
 15 out in the presence of a suitable coupling agent (e.g., benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (e.g., diisopropylcarbodiimide (DIC), PyBOP®, EDC, HBTU, DCC, or the like) and acylation catalyst (e.g., *N,N*-diisopropylethylamine, triethylamine, 4-dimethylaminopyridine, 1-hydroxybenzotriazole hydrate, or the like) in a suitable solvent (e.g., methylene chloride,

DMF, or the like) and requires approximately 3 to 20 hours to complete. Deprotection can be effected by any means which removes the protecting group and gives the desired product in reasonable yield. The reaction between the compound of Formula 6(a) or 6(b) is carried out with a suitable coupling agent and acylation catalyst. A detailed description of the

5 preparation of a compound of the formula $R^1\text{-SS}$ according to the above-described procedures is set forth in Examples 2(A-C) and 4(A-C), *infra*.

Compounds of the formula $R^1\text{OH}$ can be prepared by treating a compound of formula $R^1\text{-SS}$ with a suitable acid (e.g., trifluoroacetic acid, or the like) in a suitable solvent (e.g., methylene chloride, or the like). Alternatively, compounds of the formula $R^1\text{OH}$ in which X^1

10 is $-\text{C}(\text{O})-$ and X^2 is $-\text{CHR}^9$ can be prepared by alkylating an organometallic compound of Formula 7(a) or 7(b):



with a compound of the formula $R^9\text{L}$, in which L is a leaving group and each X^3 , X^4 , R^5 , R^6 , R^7 and R^9 are as defined for Formula I in the Summary of the Invention, and then converting

15 the resulting ethyl ester to the corresponding acid. The alkylation is carried out in a suitable solvent (e.g., THF) at -78°C to 0°C and requires 1 to 2 hours to complete. Conversion the acid can be effected by treating the ester with lithium hydroxide for approximately 15 hours. The organometallic compound is generated by treating a corresponding organo compound with an appropriate base (e.g., *N,N*-diisopropylethylamine, triethylamine, and the like) and

20 *n*-butyllithium or *tert*-butyllithium at -80 to -70°C , preferably at about -78°C , for approximately 30 minutes to an hour. A detailed description of the preparation of a compound of the formula $R^1\text{OH}$ according to the above-described procedures is set forth in Example 3, *infra*.

Examples:

REFERENCE 1Lithium 2S-amino-3-cyclohexylpropionate

A solution of methyl 2S-amino-3-cyclohexylpropionate hydrochloride (8.03 mmol, 1 eq) in dichloromethane (80 mL) and saturated NaHCO₃ solution (80 mL) was cooled to 0° C and then the organic layer was treated with a solution of 1.93 M phosgene in toluene (8.3 mL, 2 eq). The mixture was stirred for 10 minutes and then the aqueous was separated and extracted with dichloromethane (3x 27 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A portion of the residue (767 μM, 1.0 eq) was stirred under nitrogen together with morpholine (767 μM, 1.0 eq) in dry THF (1 mL) for 12 hours. The mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (1 mL). The solution was washed with water (3 x 1 mL), dried over sodium sulfate and concentrated. The residue was dissolved in methanol (2 mL) and water (37 μL) and the solution was treated with lithium hydroxide monohydrate (19 mg, 1.05 eq) and then stirred for 12 hours. The solution was adjusted to pH 11 with additional lithium hydroxide monohydrate, heated at 60° C for 4 hours and then the concentrated *in vacuo* to provide lithium 2S-morpholin-4-ylcarbonylamino-3-cyclohexylpropionate.

Proceeding as in Reference 1 provided the following compounds:

lithium 2S-piperidin-1-ylcarbonylamino-3-cyclohexylpropionate;

lithium

20 2S-(4-*tert*-butoxycarbonylpiperazin-1-ylcarbonylamino)-3-cyclohexylpropionate;

lithium 2S-(4-benzylpiperazin-1-ylcarbonylamino)-3-cyclohexylpropionate;

lithium 2S-(4-ethoxycarbonylpiperazin-1-ylcarbonylamino)-3-cyclohexylpropionate;

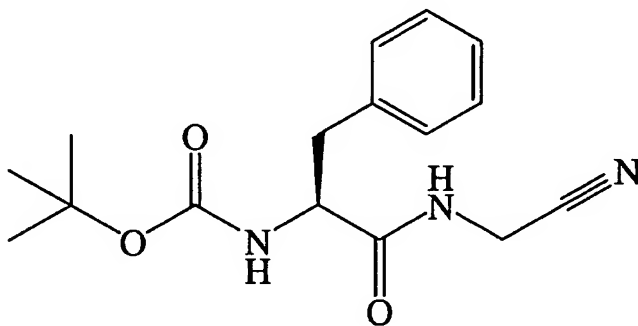
lithium 2S-(4-fur-2-ylcarbonylpiperazin-1-ylcarbonylamino)-3-cyclohexylpropionate;

REFERENCE 23-Cyclohexyl-2S-(3-methoxybenzyloxycarbonylamino)propionic acid

- A mixture of 2S-amino-3-cyclohexylpropionic acid (2.95 mmol, 1.0 eq) and sodium hydroxide (5.9 mmol, 2 eq) in a 1:1 mixture of THF/water (14 mL) was treated with
- 5 3-methoxybenzyloxyformyl chloride (2.95 mmol, 1.0 eq), stirred for 3 hours and then treated with *N,N*-diethyl ethylenediamine (2.95 mmol, 1.0 eq). The mixture was stirred for approximately 12 hours, adjusted to pH 2 with 1M hydrochloric acid solution (13 mL) and then extracted with ethyl acetate (2 x 9 mL). The extract was washed with 1M hydrochloric acid solution (6 mL), dried over sodium sulfate and concentrated to provide
- 10 3-cyclohexyl-2S-(3-methoxybenzyloxycarbonylamino)propionic acid as a yellow oil.

EXAMPLE 1*tert*-Butyl 1S-cyanomethylcarbamoyl-2-phenylethylcarbamate

(Compound 1)



- 15 A mixture comprised of 2S-*tert*-butoxycarbonylamino-3-phenylpropionic acid (28.9 g, 0.109 mol), aminoacetonitrile hydrochloride (10.1 g, 0.109 mol), triethylamine (61 mL, 0.436 mol), DMF (40 mL) and acetonitrile (360 mL) was stirred at room temperature for 27 hours. The mixture was filtered, concentrated to a volume of 100 mL and poured into ice water (1000 mL). The mixture was stirred until a precipitate had formed. The precipitate
- 20 was collected, washed with water and dried. The dry product was recrystallized from 55% ethanol/water (80 mL). The crystals were collected and recrystallized from 65%

ethanol/water (70 mL). The crystals were collected and dried to provide tert-butyl 1S-cyanomethylcarbamoyl-2-phenylethylcarbamate (20.3g, 0.067 mol) as white needles ; ¹H NMR: δ 1.39 (s, 9H), δ 3.06 (d, 2H, J = 7 Hz), δ 4.08 (m, 2H), δ 4.34 (dd, 1H, J = 13, 7 Hz), δ 4.97 (d, 1H, J = 8 Hz), δ 6.59 (m, 1H), δ 7.23 (m, 5H); ES-MS m/z 304 (MH+).

5 Proceeding as in Example 1 provided the following compounds of Formula I:

benzyl 5S-tert-butoxycarbonylamino-5-cyanomethylcarbamoylpentylcarbamate (Compound 2); ¹H NMR: δ 1.37 (m, 15 H), δ 1.63 (m, 1H), δ 1.78 (m, 1H), δ 3.14 (dd, 2H, J = 13, 6 Hz), δ 4.07 (m, 2H), δ 5.06 (s, 2H), δ 5.42 (br s, 1H), δ 7.32 (m, 5H), δ 7.48 (br s, 1H); ES-MS m/z 419 (MH+);

cyclohexyl 3S-tert-butoxycarbonylamino-N-cyanomethylsuccinamate (Compound 3); ¹H NMR: δ 1.35 (m, 17 H), δ 1.72 (m, 1H), δ 1.83 (m, 1H), δ 2.66 (dd, 1H, J = 18, 7 Hz), δ 2.96 (dd, 1H, J = 18, 5 Hz), δ 4.15 (dd, 2H, J = 6, 2 Hz), δ 4.50 (m, 1H), δ 4.77 (m, 1H), δ 5.64 (br s, 1H), δ 7.11 (br s, 1H); ES-MS m/z 354 (MH+);

15 tert-butyl 1S-cyanomethylcarbamoyl-2-(1-formyl-1H-indol-3-yl)ethylcarbamate (Compound 4); ¹H NMR: δ 1.44 (s, 9H), δ 3.23 (m, 2H), δ 4.08 (m, 2H), δ 4.46 (m, 1H), δ 4.95 (br s, 1H), δ 7.38 (m, 4H), δ 7.62 (br s, 1H); ES-MS m/z 371 (MH+);

tert-butyl 2-(3-benzyloxymethyl-3H-imidazol-4-yl)-1S-cyanomethylcarbamoylethylcarbamate (Compound 5); ¹H NMR: δ 1.39 (s, 9H), δ 3.09 (d, 2H, J = 7 Hz), δ 4.00 (d, 2H, J = 6 Hz), δ 4.42 (m, 1H), δ 4.45 (s, 2H), δ 5.29 (m, 2H), δ 5.58 (br d, 1H, J = 8 Hz), δ 6.79 (s, 1H), δ 7.29 (m, 1H), δ 7.49 (s, 1H), δ 7.93 (br s); ES-MS m/z 414 (MH+);

tert-butyl 2-(4-benzyloxyphenyl)-1S-cyanomethylcarbamoylethylcarbamate (Compound 6); ¹H NMR: δ 1.40 (s, 9H), δ 3.01 (t, 2H, J = 6 Hz), δ 4.07 (t, 2H, J = 6 Hz), δ 4.29 (m, 1H), δ 4.90 (br s, 1H), δ 5.02 (s, 2H), δ 6.40 (br s, 1H), δ 6.92 (d, 2H, J = 8 Hz), δ 7.09 (d, 2H, J = 8 Hz), δ 7.37 (m, 5H); ES-MS m/z 410 (MH+); and

tert-butyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate (Compound 7); ¹H NMR: δ 0.94 (m, 2H), δ 1.20 (m, 3H), δ 1.44 (m, 11H), δ 1.71 (m, 6H), δ 4.15 (m, 2H),

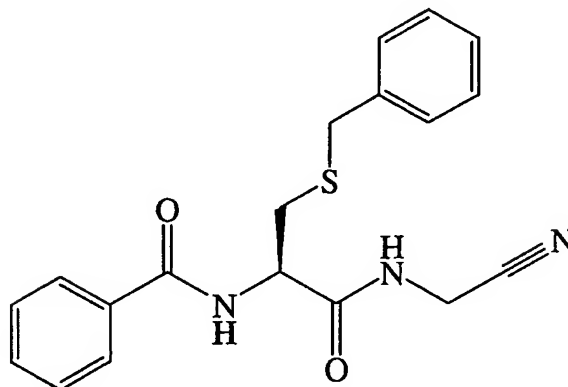
δ 4.30 (m, 1H), δ 4.87 (br s, 1H), δ 7.04 (br s); ES-MS m/z 210 (M-BuCO₂).

EXAMPLE 2

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoyl)ethyl)benzamide

(Compound 8)

5



A mixture comprised of 2*R*-benzoylamino-3-benzylsulfanylpropionic acid (0.508 g, 1.61 mmol), aminoacetonitrile hydrochloride (0.149 g, 1.61 mmol), PyBOP® (0.838 g, 1.61 mmol), *N,N*-diisopropylethylamine (0.84 mL, 4.83 mmol) and DMF (10 mL) was stirred at
10 room temperature for 2.5 hours. The mixture was concentrated and the residue was taken up into dichloromethane. The dichloromethane mixture was washed with 1N hydrochloric acid, water and aqueous sodium bicarbonate, dried (MgSO₄), filtered and concentrated. Product was purified from the residue by silica gel chromatography using 5% methanol in dichloromethane to provide *N*-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoyl)ethyl)benzamide
15 (541 mg, 1.53 mmol) as an oil. MS: m/e 353.8 (theory 353.1); Proton NMR Spectrum (DMSO- d_6): δ 8.85 (t, 1H), δ 8.75 (d, 1H), δ 7.99 (d, 2H), 7.5 (m, 3H), δ 7.3 (m, 5H), δ 4.7 (m, 1H), δ 4.15 (d, 2H), δ 3.75 (s, 2H), δ 2.8 (m, 2H) ppm.

Proceeding as in Example 2 provided the following compounds of Formula I:

N-[1*R*-cyanomethylcarbamoyl-2-(4-methylbenzylthioethyl)]benzamide

(Compound 9); MS: m/e 367.9 (theory 367.1); NMR Spectrum (DMSO- d_6): δ 8.82 (t, 1H), δ 8.69 (d, 1H), δ 7.88 (d, 2H), δ 7.5 (m, 3H), δ 7.16 (d, 2H), δ 7.08 (d, 2H), δ 4.7 (m, 1H), δ 4.2 (d, 2H), δ 3.7 (s, 2H), δ 2.75 (m, 2H), δ 2.1 (s, 3H) ppm;

N-[1*R*-cyanomethylcarbamoyl]-2-(4-methoxybenzylthioethyl)benzamide

- 5 (Compound 10); MS: m/e 383.9 (theory 383.1); NMR Spectrum (DMSO- d_6): δ 8.8 (t, 1H) δ 8.65 (d, 1H) δ 7.9 (d, 2H), δ 7.5 (m, 3H), δ 7.25 (d, 2H), δ 6.8 (d, 2H), δ 4.7 (m, 1H) δ 4.2 (d, 2H), δ 3.7 (s, 3H), δ 3.3 (s, 2H), δ 2.8 (m, 2H) ppm;

N-[2-benzyloxy-1*S*-cyanomethylcarbamoyl]ethylbenzamide (Compound 11); MS:

- m/e 337.8 (theory 337.1); NMR Spectrum (DMSO- d_6): δ 8.82 (t, 1H) δ 8.67 (d, $J = 7.8$ Hz, 1H) δ 7.91 (d, $J = 7$ Hz, 2H), δ 7.5 (m, 3H), δ 7.3 (m, 5H), δ 4.8 (m, 1H) δ 4.54 (s, 2H), δ 4.17 (d, 2H), δ 3.7 (m, 2H) ppm;

benzyl 1-cyanomethylcarbamoyl-3-methylthiopropylcarbamate (Compound 12); MS:

m/e 321.8 (theory 321.1); NMR Spectrum (DMSO- d_6): δ 8.7 (t, 1H) δ 7.6 (d, 1H) δ 7.3 (m, 5H), δ 5.0 (q, 2H), δ 4.1 (m, 3H), δ 3.3 (d, 2H), δ 2.4 (m, 2H), δ 1.9 (s, 3H) ppm;

- 15 *N*-[1*S*-cyanomethylcarbamoyl]-3-methylthiopropylbenzamide (Compound 13); MS: m/e 291.7 (theory 291.1); NMR Spectrum (DMSO- d_6): δ 8.7 (t, $J = 5.6$ Hz, 1H), δ 8.6 (d, $J = 7.7$ Hz, 1H), δ 7.9 (m, 2H), δ 7.5 (m, 3H), δ 4.5 (m, 1H), δ 4.11 (d, $J = 5.6$ Hz, 2H), δ 2.5 (m, 2H), δ 2.03 (s, 3H), δ 2.0 (m, 2H) ppm;

benzyl 2-benzylthio-1*R*-cyanomethylcarbamoylthylcarbamate (Compound 14); MS:

- 20 m/e 383.8 (theory 383.1); NMR Spectrum (DMSO- d_6): δ 8.8 (t, 1H), δ 7.8 (d, 1H), δ 7.4 (m, 10H), δ 5.1 (q, 2H), δ 4.1 (m, 1H), δ 4.2 (s, 2H), δ 3.8 (s, 2H), δ 2.8 (m, 1H), δ 2.6 (m, 1H) ppm;

methyl 4-benzyloxycarbonylamino-4*S*-cyanomethylcarbamoylbutyrate

- (Compound 15); MS: m/e 333.6 (theory 333.1); NMR Spectrum (DMSO- d_6): δ 8.7 (t, 1H), δ 7.7 (d, 1H), δ 7.4 (m, 5H), δ 5.0 (q, 2H), δ 4.0 (m, 1H), δ 3.55 (s, 3H), δ 3.3 (d, 2H), δ 2.3 (t, 2H), δ 1.8 (m, 2H) ppm;

tert-butyl 2-benzyloxy-1*S*-cyanomethylcarbamoylthylcarbamate (Compound 16);

MS: $m/e + Na$ 355.7 (theory 355.1); NMR Spectrum (DMSO- d_6): δ 8.7 (t, 1H), δ 7.0 (d, 1H), δ 7.3 (m, 5H), δ 4.45 (s, 2H), δ 4.2 (m, 1H), δ 4.1 (d, 2H), δ 3.55 (m, 2H), δ 1.4 (s,

9H) ppm;

benzyl 2-benzyloxy-1S-cyanomethylcarbamoyl ethylcarbamate (Compound 17);

NMR Spectrum (DMSO- d_6): δ 8.8 (t, 1H), δ 7.7 (d, 1H), δ 7.4 (m, 10H), δ 5.0 (q, 2H), δ 4.5 (s, 2H), δ 4.3 (m, 1H), δ 4.1 (s, 2H), δ 3.6 (m, 2H) ppm;

- 5 N-(1-cyanomethylcarbamoylpent-3-ynyl)benzamide (Compound 18); MS: m/e 269.7 (theory 269.1); NMR Spectrum (DMSO- d_6): δ 8.8 (t, 1H), δ 8.65 (d, 1H), δ 7.9 (d, 2H), δ 7.5 (m, 3H), δ 4.5 (m, 1H), δ 4.1 (d, 2H), δ 2.5 (m, 2H), δ 1.7 (s, 3H) ppm;

N-(1S-cyanomethylcarbamoyl-2-naphthalen-1-ylethyl)benzamide (Compound 19);

- ^1H NMR: δ 3.45 (dd, 1H, J = 14, 9 Hz), δ 3.73 (dd, 1H, J = 17, 6 Hz), δ 3.90 (dd, 1H, J = 19, 6 Hz), δ 4.04 (dd, 1H, J = 14, 6 Hz), δ 4.98 (m, 1H), δ 6.67 (m, 1H), δ 6.93 (m, 1H), δ 7.46 (m, 9H), δ 7.74 (m, 2H), δ 8.23 (d, 1H, J = 8 Hz); ES-MS m/z 358 (MH+);

N-[2-(4-chlorophenyl)-1S-cyanomethylcarbamoyl ethyl]benzamide (Compound 20);

- ^1H NMR: δ 3.19 (m, 2H), δ 3.96 (dd, 1H, J = 19, 4 Hz), δ 4.10 (dd, 1H, J = 20, 6 Hz), δ 4.98 (m, 1H), δ 6.79 (d, 1H, J = 7 Hz), δ 7.07 (m, 2H), δ 7.22 (m, 2H), δ 7.43 (m, 4H), δ 7.69 (m, 1H), δ 8.08 (d, 1H, J = 8 Hz); ES-MS m/z 342 (MH+);

N-(1S-cyanomethylcarbamoyl)-2-naphthalen-2-ylethylbenzamide (Compound 21);

- ^1H NMR: δ 3.29 (d, 2H, J = 7 Hz), δ 3.81 (dd, 2H, J = 18, 6 Hz), δ 3.98 (dd, 1H, J = 18, 6 Hz), δ 5.09 (dd, 1H, J = 15, 7 Hz), δ 6.74 (br d, 1H, J = 7 Hz), δ 7.37 (m, 6H), δ 7.68 (m, 6H); ES-MS m/z 358 (MH+);

- 20 N-[1-cyanomethylcarbamoyl-2-(4-cyanophenyl)ethyl]benzamide (Compound 22); ^1H NMR: δ 3.18 (dd, 1H, J = 14, 7 Hz), δ 3.30 (dd, 1H, J = 15, 7 Hz), δ 4.03 (dd, 1H, J = 17, 6 Hz), δ 4.15 (dd, 1H, J = 19, 6 Hz), δ 4.93 (dd, 1H, J = 15, 8 Hz), δ 6.81 (d, 1H, J = 10 Hz), δ 7.30 (m, 2H), δ 7.43 (m, 3H), δ 7.55 (m, 2H), δ 7.67 (d, 2H, J = 8 Hz); ES-MS m/z 333 (MH+);

- 25 N-(1S-cyanomethylcarbamoyl-2-[4-(2,6-dichlorobenzyloxy)phenyl]ethyl)benzamide (Compound 23); ^1H NMR: δ 3.15 (m, 2H), δ 4.08 (t, 2H, J = 6 Hz), δ 4.84 (dd, 1H, J = 16, 7 Hz), δ 5.24 (m, 3H), δ 6.87 (d, 1H, J = 8 Hz), δ 6.98 (m, 4H), δ 7.18 (d, 2H, J = 9 Hz), δ 7.32 (m, 4H), δ 7.78 (d, 2H, J = 8 Hz); ES-MS m/z 482 (MH+);

cyclohexyl 4-benzoylamino-4S-cyanomethylcarbamoylbutyrate (Compound 24); ^1H

NMR: δ 1.37 (m, 5H), δ 1.53 (m, 2H), δ 1.68 (m, 2H), δ 1.83 (m, 1H), δ 2.17 (m, 2H), δ 2.42 (m, 1H), δ 2.66 (m, 1H), δ 4.15 (m, 2H), δ 4.68 (m, 2H), δ 7.47 (m, 3H), δ 7.79 (m, 2H); ES-MS m/z 372 (MH⁺);

N-[2-(4-benzoylphenyl)-1*S*-cyanomethylcarbamoyl-ethyl]benzamide (Compound 25);

5 ¹H NMR: δ 3.27 (m, 2H), δ 4.00 (dd, 1H, J = 15, 6 Hz), δ 4.13 (m, 1H, J = 17, 6 Hz), δ 4.23 (d, 1H, J = 6 Hz), δ 4.97 (dd, 1H, J = 15, 8 Hz), δ 6.96 (d, 1H, J = 9 Hz), δ 7.46 (m, 9H), δ 7.71 (m, 5H); ES-MS m/z 412 (MH⁺);

N-(1*S*-cyanomethylcarbamoyl-2-phenylethyl)benzamide (Compound 26); ¹H NMR:

10 δ 3.15 (dd, 1H, J = 12, 6 Hz), δ 3.25 (dd, 1H, J = 15, 6 Hz), δ 4.08 (t, 2H, J = 6 Hz), δ 4.84 (dd, 1H, J = 15, 6 Hz), δ 6.68 (br s, 1H), δ 6.77 (br s, 1H), δ 7.29 (m, 5H), δ 7.41 (m, 2H), δ 7.53 (m, 1H), δ 7.67 (d, 2H, J = 9 Hz); ES-MS m/z 308 (MH⁺);

N-[1*S*-cyanomethylcarbamoyl-2-(1*H*-indol-3-yl)ethyl]benzamide (Compound 27);

15 ¹H NMR: δ 3.25 (dd, 1H, J = 16, 8 Hz), δ 3.52 (dd, 1H, J = 16, 6 Hz), δ 3.95 (dd, 1H, J = 18, 4 Hz), δ 4.07 (dd, 1H, J = 18, 6 Hz), δ 4.93 (m, 1H), δ 6.44 (br s, 1H), δ 6.85 (d, 1H, J = 5 Hz), δ 7.22 (m, 3H), δ 7.38 (m, 3H), δ 7.50 (m, 1H), δ 7.67 (m, 2H, J = 8 Hz), δ 7.74 (d, 1H, J = 8 Hz), δ 8.18 (br s, 1H); ES-MS m/z 347 (MH⁺);

N-[1*S*-cyanomethylcarbamoyl-2-(4-fluorophenylethyl)]benzamide (Compound 28);

20 ¹H NMR: δ 3.15 (m, 2H), δ 3.97 (dd, 1H, J = 18, 6 Hz), δ 4.11 (dd, 1H, J = 18, 6 Hz), δ 4.90 (dd, 1H, J = 15, 8 Hz), δ 6.95 (m, 3H), δ 7.20 (m, 2H), δ 7.46 (m, 3H), δ 7.68 d, 1H, J = 8 Hz); ES-MS m/z 326 (MH⁺);

N-[2-(2-chlorophenyl)-1*S*-cyanomethylcarbamoyl-ethyl]benzamide (Compound 29);

¹H NMR: δ 3.34 (m, 2H), δ 4.04 (dd, 1H, J = 16, 6 Hz), δ 4.17 (dd, 1H, J = 16, 6 Hz), δ 4.93 (dd, 1H, J = 16, 6 Hz), δ 6.85 (m, 1H), δ 7.24 (m, 4H), δ 7.44 (m, 3H), δ 7.72 (m, 2H); ES-MS m/z 342 (MH⁺);

25 *N*-[1*S*-cyanomethylcarbamoyl-2-(4-methoxyphenylethyl)]benzamide

(Compound 30); ¹H NMR: δ 3.13 (m, 2H), δ 3.76 (m, 4H), δ 4.06 (dd, 1H, J = 11, 6 Hz), δ 4.80 (m, 1H), δ 6.83 (m, 4H), δ 7.16 (d, 1H, J = 9 Hz), δ 7.46 (m, 2H), δ 7.66 (m, 2H); ES-MS m/z 338 (MH⁺);

N-[2-(4-benzoyloxyphenyl)-1-cyanomethylcarbamoyl-ethyl]benzamide

(Compound 31); ^1H NMR: δ 3.07 (m, 2H), δ 3.90 (m, 1H), δ 4.02 (m, 1H), δ 4.94 (s, 2H), δ 4.95 (m, 1H), δ 6.70 (m, 1H), δ 6.85 (m, 2H), δ 7.09 (m, 2H), δ 7.38 (m, 7H), δ 7.72 (m, 3H); ES-MS m/z 414 (MH $^+$);

benzyl *N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)isophthalamate

5 (Compound 32); ^1H NMR: δ 0.86 (m, 2H), δ 1.09 (m, 2H), δ 1.39 (m, 5H), δ 1.67 (m, 4H), δ 3.04 (m, 1H), δ 3.63 (m, 1H), δ 4.11 (m, 1H), δ 4.60 (m, 1H), δ 4.77 (m, 1H), δ 5.33 (s, 2H), δ 7.38 (m, 5H), δ 8.01 (d, 1H, $J = 9$ Hz), δ 8.14 (m, 2H), δ 8.45 (d, 1H, $J = 12$ Hz); ES-MS m/z 448 (MH $^+$);

benzyl *N*-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)terephthalamate

10 (Compound 33); ^1H NMR: δ 0.89 (m, 2H), δ 1.13 (m, 3H), δ 1.38 (m, 4H), δ 1.66 (m, 4H), δ 3.10 (m, 1H), δ 3.64 (m, 1H), δ 4.10 (m, 1H), δ 4.80 (dd, 1H, $J = 15, 8$ Hz), δ 5.34 (d, 2H, $J = 2$ Hz), δ 7.37 (m, 5H), δ 7.84 (d, 2H, $J = 7$ Hz), δ 8.03 (m, 2H); ES-MS m/z 448 (MH $^+$);

N-[1-cyanomethylcarbamoyl-2-(2-fluorophenyl)ethyl]benzamide (Compound 34); ^1H

15 NMR: δ 3.23 (m, 2H), δ 4.06 (dd, 1H, $J = 18, 6$ Hz), δ 4.15 (dd, 1H, $J = 18, 6$ Hz), δ 4.91 (dd, 1H, $J = 15, 8$ Hz), δ 7.01 (m, 2H), δ 7.23 (m, 1H), δ 7.41 (m, 2H), δ 7.52 (m, 2H), δ 7.68 (d, 2H, $J = 8$ Hz); ES-MS m/z 326 (MH $^+$);

N-(2-benzylthio-1*R*-cyanomethylcarbamoyl-2-(3,5-dimethoxyphenyl)thiazole-4-carboxamide (Compound 35); MS: Calcd. 496; Found $M + 1 = 497$;

20 *N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl-2-(3,5-dimethoxyphenyl)thiazole-4-carboxamide (Compound 36); MS: Calcd. 456; Found $M + 1 = 457$;

N-(1-cyanomethylcarbamoylpent-3-enyl)benzamide (Compound 37); MS: m/e 271.8
(theory 271.1); NMR Spectrum (DMSO- d_6): δ 8.7 (t, 1H), δ 8.657 (d, 1H), δ 7.9 (d, 2H), δ 7.5 (m, 3H), δ 5.4 (m, 2H), δ 4.5 (m, 1H), δ 4.1 (d, 2H), δ 2.5 (m, 2H), δ 2.6 (d, 3H)
25 ppm;

4-*tert*-butyl-*N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

(Compound 38); ^1H NMR (CDCl_3): δ 8.02 (br s, 1H), δ 7.73 (d, 2H, $J = 8.7$ Hz), δ 7.43 (d, 2H, $J = 8.5$ Hz), δ 7.05 (br d, 1H, $J = 8.5$ Hz), δ 4.79 (dd, 1H, $J = 15.1, 8.7$ Hz), δ 4.10 (dd, 2H, $J = 19.9$ Hz, 5.6 Hz), δ 1.51 - 1.82 (m, 5H), δ 1.30 (s, 9H), δ 0.83 - 1.72 (m, 8H);

EI MS ($M^+ = 369.9$);

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)pyrimidine-5-carboxamide

(Compound 39); ^1H NMR (CDCl_3): δ 9.33 (s, 1H), δ 8.77 (s, 1H), δ 8.56 (s, 1H), δ 8.14 (br d, 1H, $J = 8.7$ Hz), δ 7.30 (br s, 1H), δ 4.69 (dd, 1 H, $J = 14.9, 9.2$ Hz), δ 4.15 (t, 2 H, $J = 3.9$ Hz), δ 0.76-2.30 (m, 13H); EI MS ($M^+ = 315.9$);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)naphthalene-1-carboxamide

(Compound 40); ^1H NMR (CDCl_3): δ 8.19 (br d, 1H, $J = 10.0$ Hz), δ 7.81 - 7.96 (m, 3H), δ 7.47 - 7.62 (m, 3H), δ 7.35 - 7.44 (m, 1H), δ 6.69 (d, 1H, $J = 8.7$ Hz), δ 4.90 (dd, 1H, $J = 15.4, 9.0$), δ 4.03 (d, 2H, $J = 4.9$ Hz), δ 0.79 - 1.89 (m, 13H); EI MS ($M^+ = 364.0$);

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-fluorobenzamide

(Compound 41); ^1H NMR (CDCl_3): δ 7.70 - 7.83 (m, 2H), δ 7.43 (br s, 1H), δ 7.11 (t, 2H, $J = 8.7$ Hz), δ 6.66 (br d, 1H, $J = 8.5$ Hz), δ 4.69 (dd, 1H, $J = 15.5, 9.4$ Hz), δ 4.14 (dd, 2H, $J = 19.6, 8.4$ Hz), δ 0.67 - 1.88 (m, 13H); EI MS ($M^+ = 331.6$);

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-hydroxybenzamide

(Compound 42); ^1H NMR (CDCl_3): δ 7.64 (d, 2 H, $J = 9.0$ Hz), δ 7.39 (br s, 1 H), δ 6.83 (d, 2 H, $J = 9.5$ Hz), δ 6.43 (br d, 1 H, $J = 11.2$ Hz), δ 4.64 (dd, 1 H, $J = 16.8, 5.6$ Hz), δ 4.14 - 4.09 (m, 2 H), δ 0.81 - 1.89 (m, 13 H); EI MS ($M^+ = 329.8$);

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)naphthalene-2-carboxamide

(Compound 43); ^1H NMR (CDCl_3): δ 8.29 (s, 1 H), δ 7.76 - 7.94 (m, 5 H), δ 7.51 - 7.61 (m, 2 H), δ 6.57 (br d, 1 H, $J = 19.6$ Hz), δ 4.73 (dd, 1 H, $J = 19.6, 11.2$ Hz), δ 4.17 (dd, 2 H, $J = 13.3, 8.4$ Hz), δ 0.80 - 2.03 (m, 13 H); EI MS ($M^+ = 363.9$);

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-trifluoromethylbenzamide

(Compound 44); ^1H NMR (CDCl_3): δ 7.86 - 7.91 (m, 2 H), δ 7.70 - 7.75 (m, 2 H), δ 6.85 (br s, 1H), δ 6.48 (br d, 1 H, $J = 8.4$ Hz), δ 4.65 (dd, 1 H, $J = 19.6, 11.2$ Hz), δ 4.09 - 4.20 (m, 2 H), δ 0.86 - 1.74 (m, 13 H); EI MS ($M^+ = 381.9$);

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-methoxybenzamide

(Compound 45); ^1H NMR (CDCl_3): δ 7.70 - 7.73 (m, 3H), δ 6.94 (d, 2H, $J = 8.5$ Hz), δ 6.29 (br s, 1H), δ 4.57 - 4.69 (m, 1H), δ 4.08 - 4.17 (m, 2H), δ 3.85 (s, 3H), δ 0.78 - 1.73 (m, 13H); EI MS ($M^+ = 343.9$);

N-cyanomethyl-3-cyclohexyl-2S-methylsulfonylaminopropionamide (Compound 46);

¹H NMR (CDCl₃): δ 7.05 (br s, 1H), δ 5.29 (br d, 1H, J = 8.7 Hz), δ 4.12 - 4.20 (m, 1H),
δ 3.44 (d, 2H, J = 9.7 Hz), δ 3.01 (s, 3H), δ 0.81 - 1.92 (m, 13H);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)acetamide (Compound 47); ¹H

5 NMR (CDCl₃): δ 7.51 (br s, 1H), δ 6.15 (br d, 1H, J = 8.0 Hz), δ 4.49 (dd, 1H, J = 17.8,
11.4 Hz), δ 4.11 (t, 2H, J = 18.6 Hz), δ 2.02 (s, 3H), δ 0.72 - 1.80 (m, 13H); EI MS
(M⁺ = 251.6);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-fluorobenzamide (Compound 48);

¹H NMR (CDCl₃): δ 7.19 - 7.55 (m, 5 H), δ 6.72 (br s, 1 H, J = 8.7 Hz), δ 4.69 (dd, 1 H,
10 J = 10.8, 3.8 Hz), δ 4.14 (dd, 2 H, J = 2.8, 15.7 Hz), δ 0.86 - 1.86 (m, 13 H); EI MS
(M⁺ = 331.9);

4-chloro-N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

(Compound 49); ¹H NMR (CDCl₃): δ 8.78 (br s, 1H), δ 8.58 (br d, 1H, J = 8.0 Hz), δ 7.85
(d, 2H, J = 9.0 Hz), δ 7.48 (d, 2H, J = 9.2 Hz), δ 4.64 (dd, 1H, J = 7.4, 14.1 Hz), δ 4.16
15 (dd, 2H, J = 3.1, 6.1 Hz), δ 0.87 - 1.85 (m, 13 H); EI MS (M⁺ = 347.9);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-trifluoromethylbenzamide

(Compound 50); ¹H NMR (CDCl₃): δ 7.42 - 7.78 (m, 5 H), δ 6.56 (br d, 1 H, J = 9.0 Hz),
δ 4.81 (dd, 1 H, J = 15.4, 9.2 Hz), δ 4.10 (t, 2 H, J = 5.7 Hz), δ 0.80 - 1.79 (m, 13 H); EI
MS (M⁺ = 382.0);

20 N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-fluorobenzamide (Compound 51);

¹H NMR (CDCl₃): δ 8.00 (t, 1 H, J = 8.4 Hz), δ 7.64 (br s, 1H), δ 7.50 (dd, 1H, J = 8.1,
2.5 Hz), δ 7.24 - 7.30 (m, 1 H), δ 7.07 - 7.18 (m, 2 H), δ 4.76 (dd, 1H, J = 17.2, 8.2 Hz),
δ 4.16 (dd, 2H, J = 18.0, 6.2 Hz), δ 0.81 - 1.89 (m, 13 H); EI MS (M⁺ = 331.9);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-trifluoromethoxybenzamide

25 (Compound 52); ¹H NMR (CDCl₃): δ 7.01 - 8.02 (m, 6 H), δ 4.75 (br d, 1H, J = 14.6 Hz),
δ 4.14 (dd, 2H, J = 6.0, 18.2 Hz), δ 0.78 - 1.90 (m, 13 H); EI MS (M⁺ = 398.0);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-2,6-difluorobenzamide

(Compound 53); ¹H NMR (CDCl₃): δ 7.66 (br s, 1H), δ 7.39 (t, 1H, J = 8.7 Hz), δ 6.95 (t,
2 H, J = 8.7 Hz), δ 6.74 (br d, 1 H, J = 8.5 Hz), δ 4.85 (dd, 1H, J = 14.9, 9.2 Hz),

δ 0.86 - 1.87 (m, 13 H); EI MS ($M^+ = 349.9$);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-2,3-difluorobenzamide

(Compound 54); ^1H NMR (CDCl_3): δ 8.04 (dd, 1H, $J = 15.3, 8.7$ Hz), δ 7.55 (br s, 1H), δ 6.84 - 7.07 (m, 3H), δ 4.74 (dd, 1H, $J = 16.6, 7.9$ Hz), δ 4.16 (dd, 2H, $J = 18.0, 5.9$ Hz),

5 δ 0.82 - 1.89 (m, 13H); EI MS ($M^+ = 349.9$);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-2,5-difluorobenzamide

(Compound 55); ^1H NMR (CDCl_3): δ 7.69 (m, 1H), δ 7.37 (br s, 1H), δ 7.08 - 7.27 (m, 3H), δ 4.71 (dd, 1H, $J = 15.1, 6.1$ Hz), δ 4.16 (dd, 2H, $J = 18.0, 6.2$ Hz), δ 0.84 - 1.90 (m, 13 H); EI MS ($M^+ = 350.1$);

10 *N*-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-2,4-difluorobenzamide

(Compound 56); ^1H NMR (CDCl_3): δ 7.80 (br s, 1H), δ 7.65 (t, 1H), δ 7.14 - 7.36 (m, 3H), δ 4.79 (dd, 1H, $J = 14.9, 7.2$ Hz), δ 4.15 (dd, 2H, $J = 18.2, 5.9$ Hz), δ 0.80 - 1.81 (m, 13 H); EI MS ($M^+ = 349.9$);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-3,4-dimethoxybenzamide

15 (Compound 57); ^1H NMR (CDCl_3): δ 7.66 (br s, 1H), δ 7.28 - 7.41 (m, 2 H), δ 6.86 (d, 1H, $J = 8.4$ Hz), δ 6.73 (br d, 1H, $J = 7.9$ Hz), δ 4.71 (dd, 1H, $J = 14.1, 8.4$ Hz), δ 4.14 (dd, 2H, $J = 17.3, 5.9$ Hz), δ 3.91 (s, 6 H), δ 0.81 - 1.88 (m, 13 H); EI MS ($M^+ = 374$);

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-3,5-dimethoxybenzamide

(Compound 58); ^1H NMR (CDCl_3): δ 7.41 (br s, 1H), δ 6.88 (d, 2H, $J = 2.4$ Hz), δ 6.59 (t, 2H, $J = 2.2$ Hz), δ 4.67 (dd, 1H, $J = 16.8, 3.0$ Hz), δ 4.12 (dd, 2 H, $J = 17.3, 5.7$ Hz), δ 3.81 (s, 6H), δ 0.82 - 1.88 (m, 13H); EI MS ($M^+ = 374$);

N-(1-cyanomethylcarbamoyl-2-thiazol-5-ylethyl)benzamide (Compound 59); ^1H

NMR (CDCl_3): δ 8.30 (d, 2H, $J = 8.7$ Hz), δ 7.72 (br s, 1H), δ 7.38 - 7.67 (m, 4H), δ 7.13 (t, 2H, $J = 8.0$ Hz), δ 4.96 (dd, 1H, $J = 12.3, 5.9$ Hz), δ 4.02 (t, 2H, $J = 10.5$ Hz), δ 3.48

25 (dd, 2H, $J = 15.7, 5.4$ Hz);

N-(1-cyanomethylcarbamoyl-2-thien-2-ylethyl)benzamide (Compound 60); ^1H NMR

(CDCl_3): δ 7.71 (d, 2H, $J = 8.5$ Hz), δ 7.39 - 7.55 (m, 4H), δ 7.14 (d, 1H, $J = 11.2$ Hz), δ 6.85 - 6.96 (m, 3H), δ 4.94 (dd, 1H, $J = 14.6, 6.9$ Hz), δ 4.09 (m, 2H), δ 3.41 (t, 2H, $J = 6.2$ Hz); EI MS ($M^+ = 313.8$);

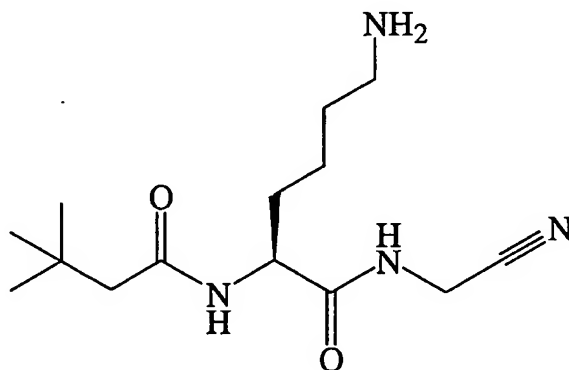
N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide (Compound 61); Proton NMR (300 MHz, CDCl₃): δ 7.79 (d, J = 7 Hz, 2H), δ 7.67 (bt, 1H), δ 7.44 (m, 3H), δ 6.75 (bd, 1H), δ 4.74 (m, 1H), δ 4.10 (m, 2H), δ 1.50 - 1.88 (m, 8H), δ 0.83 - 1.44 (m, 5H). MS (electrospray): mH⁺ 313.9 (100%); and

- 5 N-cyanomethyl-3-cyclohexyl-2S-trifluoromethylsulfonylaminopropionamide
(Compound 62).

EXAMPLE 3

tert-Butyl 5-amino-1S-cyanomethylcarbamoylpentylcarbamate
(Compound 63)

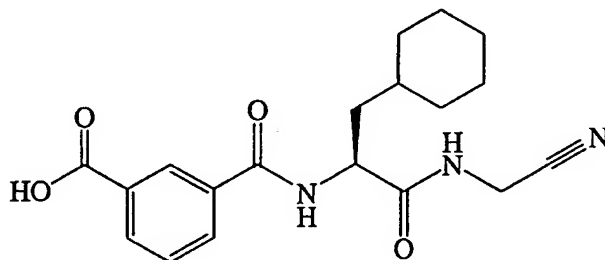
10



- A solution comprised of benzyl 5S-*tert*-butoxycarbonylamino-5-cyanomethylcarbamoylpentylcarbamate (77 mg, 184 μ mol), prepared as in Example 1, in ethanol (2 mL) was treated with ammonium formate (116 mg, 1.84 mmol) and 10% wt palladium on carbon (77 mg). The mixture was stirred for 15 hours and then filtered through
15 Celite. The filter cake washed with ethanol and the combined filtrates were concentrated on a rotary evaporator to provide tert-butyl 5-amino-1S-cyanomethylcarbamoylpentylcarbamate (61 mg, 184 μ mol) as a white solid. ¹H NMR (DMSO-d₆): δ 1.42 (m, 17 H), δ 2.63 (m, 2H), δ 3.09 (m, 2H); ES-MS m/z 323 (MK⁺).

EXAMPLE 4*N*-(1*S*-Cyanomethylcarbamoyl-2-cyclohexylethyl)isophthalamic acid

(Compound 64)



5 A solution comprised of benzyl *N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)isophthalamate (82.4 mg, 184 μ mol, 1.0 eq), prepared as in Example 2, in ethanol (2 mL) was treated with ammonium formate (116 mg, 1.84 mmol, 10.0 eq) and 10% wt palladium on carbon (82.4 mg). The mixture was stirred for 15 hours and filtered through Celite. The filter cake was washed with ethanol and the combined filtrates were concentrated
10 on a rotary evaporator to provide *N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)terephthalamic acid (61 mg, 170.7 μ mol) as a white solid. ^1H NMR (MeOH- d_4): δ 0.96 (m, 2H), δ 1.26 (m, 2H), δ 1.38 (m, 4H), δ 1.76 (m, 5H), δ 3.23 (d, 1H, $J = 8$ Hz), δ 3.72 (t, 1H, $J = 7$ Hz), δ 4.50 (m, 1H), δ 7.50 (m, 1H), δ 7.97 (m, 1H), δ 8.13 (m, 1H), δ 8.46 (m, 1H); ES-MS m/z 359 (MD+).

15 Proceeding as in Example 4 provided the following compounds of Formula I:

N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)terephthalamic acid (Compound 65);

^1H NMR (MeOH- d_4): δ 0.96 (m, 2H), δ 1.32 (m, 5H), δ 1.81 (m, 6H), δ 3.12 (m, 2H), δ 4.92 (m, 1H), δ 7.87 (m, 2H), δ 8.02 (m, 2H); ES-MS m/z 359 (MD+);

N-[1-cyanomethylcarbamoyl-2-(2,6-dichlorophenyl)ethyl]benzamide

20 (Compound 66); ^1H NMR: δ 3.45 (m, 1H), δ 3.56 (m, 1H), δ 4.13 (m, 2H), δ 5.03 (m, 1H), δ 7.30 (m, 5H), δ 7.63 (m, 3H); ES-MS m/z 376 (MH+); and

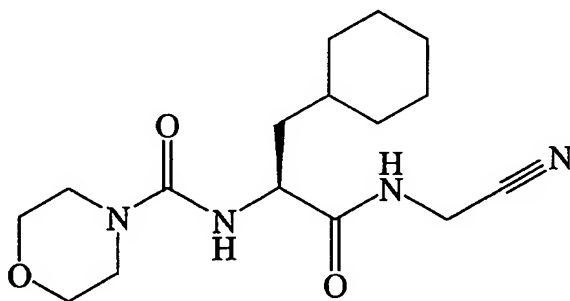
N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)phthalamic acid (Compound 67); ^1H

NMR (MeOH- d_4): δ 0.94 (d, 2H, $J = 7$ Hz), δ 0.97 (d, 2H, $J = 7$ Hz), δ 1.28 (d, 2H, $J = 7$ Hz), δ 1.47 (m, 1H), δ 1.73 (m, 6H), δ 3.09 (t, 1H; $J = 6$ Hz), δ 3.29 (m, 1H), δ 4.45 (dd, 1H, $J = 11, 5$ Hz), δ 7.36 (m, 1H), δ 7.58 (m, 2H), δ 7.72 (m, 1H); ES-MS m/z 359 (MD+).

5

EXAMPLE 5*N*-(1*S*-Cyanomethylcarbamoyl-2-cyclohexylethyl)morpholine-4-carboxamide

(Compound 68)



A mixture of lithium 2*S*-amino-3-cyclohexylpropionate (260 μ mol, 1.0 eq), provided
10 as in Reference 1, EDC (286 μ mol, 1.1 eq), HOBt (312 μ mol, 1.2 eq) and triethylamine (911
 μ mol, 3.5 eq) in dry dichloromethane (1 mL) was stirred under a nitrogen atmosphere for 5
minutes and then treated with aminoacetonitrile hydrochloride (520 μ mol, 2.0 eq). The
mixture was stirred 15 hours and then diluted with ethyl acetate (1 mL). The dilution was
washed with 1 M hydrochloric acid (2x 1 mL), saturated NaHCO_3 (1 mL) and saturated
15 NaCl (1 mL), dried over Na_2SO_4 , filtered and concentrated on a rotary evaporator to
provide *N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)morpholine-4-carboxamide. ^1H
NMR (CDCl_3) 0.95 (m, 2H); 1.23 (m, 4H); 1.62 (m, 7H); 3.35 (m, 4H); 3.68 (m, 4H); 4.05
(dd, 2H, $J = 16, 6$ Hz); 4.17 (dd, 2H, $J = 18, 6$ Hz); 4.27 (m, 1H); 5.01 (d, 1H, $J = 8$ Hz);
7.93 (t, 1H, $J = 6$ Hz); ES-MS m/z 323 (MH+).

Proceeding as in Example 5 provided the following compounds of Formula I:

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)piperidine-1-carboxamide

(Compound 69); ¹H NMR (CDCl₃) (m, 2H); 1.24 (m, 6H); 1.60 (m, 11H); 3.54 (m, 4H); 4.11 (m, 2H); 4.33 (m, 1H); 4.75 (d, 1H, J= 8 Hz); 7.88 (t, 1H, J= 6 Hz); ES-MS m/z 321 (MH+);

tert-butyl 4-(1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamoyl)piperazine-

1-carboxylate (Compound 70); ¹H NMR (CDCl₃) 0.89 (m, 2H); 1.23 (m, 4H); 1.44 (s, 9H); 1.66 (m, 7H); 3.36 (s, 4H); 3.40 (s, 4H); 4.03 (dd, 1H, J= 18, 5 Hz); 4.14 (dd, 1H, J= 18, 6 Hz); 4.38 (dd, 1H, J=15, 8 Hz); 5.32 (d, 1H, J= 8 Hz); 8.21 (t, 1H, J= 6 Hz); ES-

MS m/z 422 (MH+);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-benzylpiperazine-1-carboxamide

(Compound 71); ¹H NMR (CDCl₃) (0.96 (m, 2H); 1.24 (m, 4H); 1.70 (m, 7H); 2.44 (t, 4H, J= 5 Hz); 3.37 (t, 4H, J= 5 Hz); 3.52 (s, 2H); 4.06 (dd, 1H, J= 18, 6 Hz); 4.15 (dd, 1H, J= 18, 6 Hz); 4.32 (m, 1H); 7.30 (m, 5H); 7.72 (t, 1H, J= 6 Hz); ES-MS m/z 412 (MH+);

3-methoxybenzyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate

(Compound 72); ¹H NMR 0.96 (m, 2H); 1.24 (m, 4H); 1.70 (m, 7H); 3.78 (s, 3H); 4.12 (m, 2H); 4.21 (m, 1H); 5.11 (m, 2H); 6.89 (m, 3H); 7.32 (m, 1H); ES-MS m/z 374 (MH+);

ethyl 4-(1S-cyanomethylcarbamoyl-

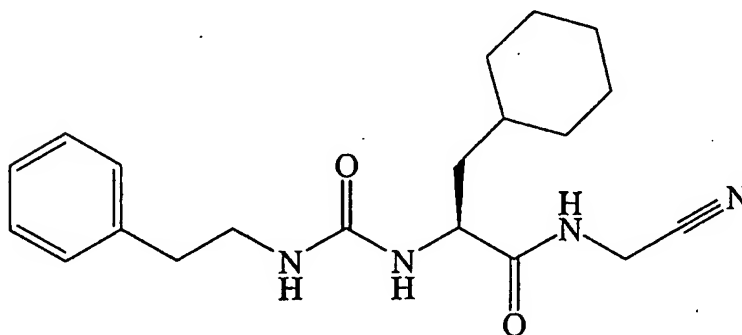
2-cyclohexylethylcarbamoyl)piperazine-1-carboxylate (Compound 73); and

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-fur-2-ylcarbonylpiperazine-

1-carboxamide (Compound 74).

EXAMPLE 6N-Cyanomethyl-3-cyclohexyl-2S-(3-phenethylureido)propionamide

(Compound 75)



- 5 A solution of *tert*-butyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate (103 mmol, 1 eq), provided as in Example 1, in diethyl ether (323 mL) was treated with toluenesulfonic acid monohydrate (206 mmol, 2.0 eq, azeotroped on a rotary evaporator with 2-propanol 3 times, until a white solid had formed) for 12 hours. The supernatant was decanted and the solid was washed extensively with diethyl ether until a powder had formed.
- 10 A portion of the resulting acid salt (789 μ mol, 1 eq) was suspended in dry acetonitrile (1 mL) and then treated with phenethylisocyanate (789 μ mol, 1.0 eq) and 4-methylmorpholine (789 μ mol, 1 eq) for 12 hours. The mixture was concentrated *in vacuo* and the residue dissolved in methylene chloride. The solution was stirred with 100 mg Argonaut PS-trisamine resin (345 μ mol, 0.4 eq) for 2 hours. The mixture was filtered, diluted with ethyl acetate (1 mL), washed with 1M hydrochloric acid (1 mL), saturated sodium bicarbonate solution and
- 15 saturated NaCl solution, dried over sodium sulfate, filtered and concentrated to provide N-cyanomethyl-3-cyclohexyl-2S-(3-phenethylureido)propionamide.

Proceeding as in Example 6 provided N-cyanomethyl-3-cyclohexyl-2S-(3-isopropylureido)propionamide (Compound 76).

Proceeding in a fashion analogous to the procedures exemplified above provided the following compounds of Formula I:

- N-[1S-cyanomethylcarbamoyl-3-phenylpropyl]benzamide (Compound 77);
N-[1S-cyanomethylcarbamoyl-2-(4-hydroxyphenylethyl)]benzamide
5 (Compound 78);
N-(1-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-hydroxybenzamide
(Compound 79); NMR 300mHz (DMSO-d₆), 8.39 (d, J=8.5H₃, 1H), 7.26 (m, 3H), 6.96
(m, 1H), 4.64 (m, 1H), 4.14 (dd, J=4.2 and 17.3H₃, 2H), 3.30 (m, 2H), 1.71 (m, 7H), 1.68-
0.80 (m, 6H); MS=329.85 M+=329.40;
- 10 1-benzyl-5-benzyloxy-N-(1-cyanomethylcarbamoyl-2-phenylethyl)-2-methyl-
1H-indole-3-carboxamide (Compound 80); MS: (m/z [mH⁺]) 557.0;
N-(1-cyanomethylcarbamoyl-2-phenylethyl)-1-furan-2-ylmethyl-5-methoxy-
2-methyl-1H-indole-3-carboxamide (Compound 81); MS: (m/z [mH⁺]) 470.6;
N-(1-cyanomethylcarbamoyl-2-methylpropyl)-5-ethoxy-1-furan-2-ylmethyl-
15 2-methyl-1H-indole-3-carboxamide (Compound 82); MS: (m/z [mH⁺]) 436.9;
1-benzo[1,3]dioxol-4-ylmethyl-N-(2-benzylsulfanyl-1-cyanomethylcarbamoylethyl)-
5-methoxy-2-methyl-1H-indole-3-carboxamide (Compound 83); MS: (m/z [mH⁺]) 570.8;
benzyl 5-(1-benzo[1,3]dioxol-4-ylmethyl-5-benzyloxy-2-methyl-
1H-indol-3-ylcarbonylamino)-5-cyanomethylcarbamoylpentylcarbamate (Compound 84);
20 MS: (m/z [mH⁺]) 716.0;
benzyl 5-(1-benzyl-5-benzyloxy-2-methyl-1H-indol-3-ylcarbonylamino)-
5-cyanomethylcarbamoylpentylcarbamate (Compound 85); MS: (m/z [mH⁺]) 672.4;
benzyl 5-cyanomethylcarbamoyl-5-(1-furan-2-ylmethyl-5-methoxy-2-methyl-
1H-indol-3-ylcarbonylamino)pentylcarbamate (Compound 86); MS: (m/z [mH⁺]) 586.8;
25 N-(1-cyanomethylcarbamoylpent-3-enyl)benzamide (Compound 87); NMR 300mHz
(DMSO-d₆), 8.67 (t, J=6H₃, 1H), 8.53 (d, J=8.5H₃, 1H), 7.86 (m, 2H), 7.50 (m, 3H), 5.3-
5.7 (m, 2H), 4.40 (m, 1H), 4.12 (d, J=6H₃, 2H), 2.3-2.6 (m, 2H), 1.57 (d, J=6.9H₃, 3H);
MS=271.8 M+=271.32;

N-(1-cyanomethylcarbamoylpent-4-enyl)benzamide (Compound 88); NMR 300mHz (DMSO-d₆), 8.66 (m, 1H), 8.57 (d, J=8.2Hz, 1H), 7.89 (m, 2H), 7.47 (m, 3H), 5.80 (m, 1H), 4.9-5.05 (m, 2H), 4.4 (m, 1H), 4.11 (d, J=2.5Hz, 2H), 2.1 (m, 2H), 1.83 (m, 2H); MS=271.8 M+=271.32;

5 N-(1-cyanomethylcarbamoylbutyl)benzamide (Compound 89); NMR 300mHz (DMSO-d₆), 8.66 (t, J=5.8Hz, 1H), 8.53 (d, J=8.8Hz, 1H), 7.90 (m, 2H), 7.46 (m, 3H), 4.41 (m, 1H), 4.12 (m, 2H), 1.70 (m, 2H), 0.87 (t, J=8Hz, 3H); MS=259.8 M+=259.31;

N-(1-cyanomethylcarbamoylpent-4-ynyl)benzamide (Compound 90); NMR 300mHz (DMSO-d₆), 8.67 (t, 1H), 8.61 (d, J=8.5Hz, 1H), 7.91 (m, 2H), 7.50 (m, 3H), 4.5 (m, 1H),
10 4.12 (m, 2H), 2.83 (t, J=2.5Hz, 1H), 2.25 (m, 2H), 1.97 (m, 2H); MS=269.8 M+=269.30;

2-chloro-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide
(Compound 91);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-iodobenzamide (Compound 92);
¹H NMR (CDCl₃): 7.68 (t, J=6Hz, 1H), 7.34 (m, 4H), 6.41 (d, J=8Hz, 1H), 4.78 (m, 1H),
15 4.13 (d, J=12Hz, 2H), 2.0-0.8 (m, 13H); MS m/e 439.9;

2-bromo-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide
(Compound 93); ¹H NMR (CDCl₃): 7.68 (t, J=5.7Hz, 1H), 7.58 (dd, J=3,12Hz, 1H), 7.44
(dd, J=2.1,12Hz, 1H), 7.34 (m, 2H), 7.57 (d, J=8Hz, 1H), 4.79 (m, 1H), 4.13 (d, J=5.7Hz,
2H), 2.0-0.8 (m, 13H); MS m/e 393.7;

20 N-(1S-cyanomethylcarbamoylhexyl)benzamide (Compound 94); ¹H NMR (DMSO):
8.65 (t, J = 3Hz, 1H), 8.54 (d, J = 8Hz, 1H), 7.91 (d, J = 7Hz, 2H), 7.5 (m, 3H), 4.4 (m, 1H),
4.13 (d, J = 5Hz, 2H), 1.74 (m, 2H), 1.3 (m, 6H), 0.85 (t, J = 7Hz, 3H); MS: m/e = 287.8;

N-(1S-cyanomethylcarbamoyl-4-phenylbutyl)benzamide (Compound 95); ¹H NMR
(DMSO): 8.67 (t, J = 7Hz, 1H), 8.56 (d, J = 9Hz, 1H), 7.88 (d, J = 9Hz, 2H), 7.4 (m, 3H),
25 7.2 (m, 5H), 4.45 (m, 1H), 4.11 (d, J = 5Hz, 2H), 2.58 (t, J = 8Hz, 2H), 1.7 (m, 4H); MS:
m/e = 335.9;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-methoxybenzamide
(Compound 96);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3,4,5-trimethoxybenzamide

(Compound 97);

benzyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate (Compound 98);

isobutyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate (Compound 99);

cyclohexylmethyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate

5 (Compound 100);

N-(1S-cyanomethylcarbamoyl-3-cyclohexylpropyl)benzamide (Compound 101); ¹H NMR (DMSO): 8.66 (m, 1H), 8.52 (d, J = 8Hz, 1H), 7.88 (d, J = 8Hz, 2H), 7.45 (m, 3H), 4.37 (m, 1H), 4.12 (m, 2H), 1.9 – 0.08 (m, 15H); MS: m/e = 328.3;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-trifluoromethoxybenzamide
10 (Compound 102); ¹H NMR (CDCl₃): 7.90 (dd, J=3, 10Hz, 1H), 7.79 (m, 1H), 7.535 (m, 1H), 7.395 (m, 1H), 7.31 (m, 1H), 6.92 (d, J=8Hz, 1H), 4.74 (m, 1H), 4.2 (dd, J=6, 17Hz, 1H), 4.1 (dd, J=6, 17Hz, 1H), 0.8-1.8 (m, 13H); MS: m/e = 397.9;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-trifluoromethoxybenzamide
(Compound 103); ¹H NMR (CDCl₃): 7.68 (m, 2H), 7.44 (m, 3H), 7.03 (t, J=6.6Hz, 1H),
15 4.73 (m, 1H), 4.38 (m, 1H), 4.11 (m, 2H), 0.8-1.8 (m, 11H); MS: m/e = 397.9;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-iodobenzamide
(Compound 104); ¹H NMR (CDCl₃): 8.1 (t, J=2.8Hz, 1H), 7.87 (d, J=6.9Hz, 1H), 7.70
(d, J=7.7Hz, 1H), 7.19 (t, J=17.5Hz, 1H), 6.9 (m, 1H), 6.44 (d, J=12Hz, 1H), 4.63 (m, 1H),
4.21 (dd, J=9.6, 6.6Hz, 1H), 4.1 (dd, J=9.6, 6.6Hz, 1H) 0.8-2.0 (m, 13H); MS: m/e = 440.0;

3-chloro-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide
20 (Compound 105); ¹H NMR (CDCl₃): 7.5 (t, J=5.2Hz, 1H), 7.65 (d, J=7.63Hz, 1H), 7.51
(d, J=6Hz, 1H), 7.39 (t, J=8.8Hz, 1H), 6.59 (d, J=9.9Hz, 1H), 2.0-0.8 (m, 13H); MS: m/e
= 348.0;

2-methoxyethyl 1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamate
25 (Compound 106);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)cyclohexanecarboxamide
(Compound 107);

N-cyanomethyl-3-cyclohexyl-2S-[2-(4-methoxyphenyl)acetylamino]propionamide
(Compound 108); ¹H NMR (CDCl₃): 7.83 (t, J=6Hz, 1H), 7.13 (d, J=9Hz, 2H), 6.86

(d, J=12Hz, 2H), 6.22 (d, J=8Hz, 1H), 4.55 (m, 1H), 3.95 (m, 2H), 3.78 (s, J=0Hz, 3H), 0.8-1.8 (m, 13H); MS: m/e = 358.0;

N-(1R-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-methylsulfanylbenzamide

(Compound 109); ¹H NMR: (CDCl₃) 8.11 (t, J=5.5Hz, 1H), 7.50 (d, J=7.5Hz, 1H), 7.40 (t, J=7.5Hz, 1H), 7.30 (d, J=1Hz, J=7.9Hz, 1H), 7.17 (t, J=7.7Hz, 1H), 6.94 (d, J=8.4Hz, 1H), 4.88 (m, 1H), 4.16 (dd, J=5.7Hz, J=17.3Hz, 1H), 4.08 (dd, J=5.7Hz, J=17.3Hz, 1H), 2.46 (s, 3H), 1.85-0.80 (m, 13H); MS: (M⁺+1) 360;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3,4-difluoro-benzamide

(Compound 110); ¹H NMR (CDCl₃): 7.5 (t, J=5.1Hz, 1H), 5.88 (d, J=7.7Hz, 1H), 4.49 (m, 1H), 4.18 d, J=6Hz, 1H), 4.11 (d, J=6Hz, 1H), 2.12-0.8 (m, 24H); MS: m/e = 320.0;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-methoxybenzamide

(Compound 111); ¹H NMR: (CDCl₃) 7.63 (m, 1H), 7.37-7.28 (m, 3H), 7.06 (m, 1H), 6.76 (d, J=7.7Hz, 1H), 4.73 (m, 1H), 4.20 (dd, J=5.9Hz, J=17.3Hz, 1H), 4.07 (dd, J=5.7Hz, J=17.3Hz, 1H), 3.83 (s, 3H), 1.85-0.82 (m, 13H); MS: (M⁺+1) 344;

4-bromo-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

(Compound 112); ¹H NMR: (CDCl₃) 7.65-7.57 (m, 4H), 7.10 (m, 1H), 6.48 (d, J=7.7Hz, 1H), 4.67 (m, 1H), 4.21 (dd, J=5.9Hz, J=17.3Hz, 1H), 4.12 (dd, J=5.7Hz, J=17.3Hz, 1H), 1.85-0.82 (m, 13H); MS: (M⁺+1) 392/394;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)piperazine-1-carboxamide

(Compound 113);

benzyl 4-(2-benzoylamino-2S-cyanomethylcarbamoylethyl)piperidine-1-carboxylate

(Compound 114);

3-bromo-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

(Compound 115); ¹H NMR: (CD₃OD) 8.05 (s, 1H), 7.83 (d, J=7.7Hz, 1H), 7.71 (d, J=7.5Hz, 1H), 7.40 (t, J=7.9Hz, 1H), 4.67 (dd, J=6.9Hz, J=8.7Hz, 1H), 4.19 (d, J=17.5Hz, 1H), 4.11 (d, J=17.3Hz, 1H), 1.85-0.82 (m, 13H); MS: (M⁺+1) 392/394;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-methylbenzamide

(Compound 116); ¹H NMR (DMSO): 7.64 (t, 1H), 7.25 (m, 4H), 6.43 (d, J=12Hz, 1H), 4.67 (m, 1H), 4.13 (m, 2H), 2.4 (s, 3H), 2.0-0.7 (m, 13H); MS m/e 327.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)pentanamide (Compound 117); ¹H NMR (CDCl₃): 8.11 (t, 1H), 6.53 (d, J=8Hz, 1H), 4.59 (m, 1H), 4.10 (m, 2H), 2.21 (t, J=4.5Hz, 2H), 1.8-0.8 (m, 20H); MS m/e 293.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-2-methylbenzamide
5 (Compound 118); ¹H NMR (CDCl₃): 7.91 (d, J=5.7Hz, 1H), 7.23 (m, 4H), 6.50 (t, J=3Hz, 1H), 4.76 (m, 1H), 4.05 (s, J=18Hz, 1H), 2.38 (d, 3H), 2.0-0.8 (m, 13H); MS m/e 328;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)thiophene-3-carboxamide
(Compound 119); ¹H NMR (CDCl₃): 8.1 (m, 2H), 7.32 (m, t, 2H), 7.08 (d, J=7.9Hz, 1H), 4.73 (m, 1H), 4.05 (dd, J=6,17Hz, 2H), 2.0-0.8 (m, 13H); MS m/e 319.80;
10 2S-[2-(4-benzyloxyphenyl)acetylaminol]-N-cyanomethyl-3-cyclohexylpropionamide
(Compound 120); ¹H NMR (CDCl₃): 7.8 (t, 1H), 7.5-6.9 (m, 9H), 6.10 (d, J=8Hz, 1H), 5.0 (s, 2H), 4.5 (m, 1H), 3.95 (m, 2H), 3.5 (s, 2H), 1.9-1.0 (m, 13H); MS m/e 434.97;

N-cyanomethyl-3-cyclohexyl-2S-[2-(2-methoxyphenyl)acetylaminol]propionamide
(Compound 121); ¹H NMR (CDCl₃): 7.58 (t, J=7.8Hz, 1H), 7.23 (m, 2H), 6.91 (m, 2H),
15 6.21 (d, J=7.2Hz, 1H), 4.44 (m, 1H), 3.94 (d, J=5.7Hz, 2H), 3.84 (s, 3H), 3.60 (d, J=8Hz, 1H), 3.49 (d, J=8Hz, 1H), 1.8-0.5 (m, 13H); MS m/e 357.89;

N-cyanomethyl-3-cyclohexyl-2-[2-(4-phenoxyphenyl)acetylaminol]propionamide
(Compound 122); ¹H NMR (CDCl₃): 7.55 (t, J=3Hz, 1H), 7.4-6.9 (m, 9H), 6.04 (d, J=8.8Hz, 1H), 4.47 (m, 1H), 4.02 (d, J=6Hz, 2H), 3.54 (s, 2H), 2.0-0.6 (m, 13H); MS m/e
20 419.94;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)isonicotinamide (Compound 123);
¹H NMR (DMSO): 8.68 (d, J=4.5Hz, 2H), 8.2 (t, J=6.3Hz, 1H), 7.85 (d, J=7.9Hz, 1H), 7.66 (d, J=4.7Hz, 2H), 4.80 (m, 1H), 4.12 (d, J=6Hz, 2H), 2.0-0.7 (m, 13H); MS m/e 314.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)thiophene-2-carboxamide
25 (Compound 124); ¹H NMR: (CDCl₃) 8.55 (t, J=5.5Hz, 1H), 7.75 (d, J=7.7Hz, 1H), 7.64 (dd, J=1Hz, J=4Hz, 1H), 7.48 (dd, J=1Hz, J=5Hz, 1H), 7.04 (dd, J=5Hz, J=4Hz, 1H), 4.82 (q, J=7.5Hz, 1H), 4.13 (dd, J=5.9Hz, J=17Hz, 1H), 3.93 (dd, J=5.7Hz, J=17Hz, 1H), 1.80-0.84 (m, 13H); MS: (M⁺+1) 319.8;

N-(1S-cyanomethylcarbamoyl-2-piperidin-4-ylethyl)benzamide (Compound 125);

N-[1S-cyanomethylcarbamoyl-2-(1-formyl-1H-indol-3-yl)ethyl]benzamide

(Compound 126);

N-[1S-cyanomethylcarbamoyl-2-(1-formyl-1H-indol-3-yl)ethyl]-4-fluorobenzamide

5 (Compound 127);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)nicotinamide (Compound 128); ¹H

NMR (CDCl₃): 9.01 (d, J=4Hz, 1H), 8.72 (m, 1H), 8.11 (m, 1H), 7.83 (t, J=3Hz, 1H), 7.39 (m, 2H), 4.77 (m, 1H), 7.14 (m, 2H), 2.0-0.6 (m, 13H); MS m/e 314.88;

tert-butyl 3-(1S-cyanomethylcarbamoyl-

10 2-cyclohexylethylcarbamoyl)phenylcarbamate (Compound 129);

N-[1S-cyanomethylcarbamoyl-

2-(1-formyl-1H-indol-3-yl)ethyl]-4-hydroxybenzamide (Compound 130);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-1H-indole-5-carboxamide

(Compound 131); ¹H NMR (CDCl₃): 11.32 (s, 1H), 8.64 (t, J=6Hz, 1H), 8.35 (d, J=9Hz, 1H), 8.22 (s, 1H), 7.68 (dd, J=3,10Hz, 1H), 7.42 (m, 1H), 6.54 (m, 1H), 4.54 (m, 1H), 4.12 (d, J=5.7Hz, 2H), 2.0-0.7 (m, 13H); MS m/e 352.86;

N-(1R-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-methylsulfanylbzamide

(Compound 132);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)-3-fluorobenzamide

20 (Compound 133); ¹H NMR (CDCl₃): 7.18-7.79 (m, 1H), 4.70 (dd, J=13.3, 7.2Hz, 1H), 4.28 (d, J=7.7Hz, 1H), 4.22 (d, J=7.4Hz, 1H), 3.78 (m, 2H), 3.03 (dd, J=14.1, 6.2Hz, 1H), 2.84 (J=14.1, 7.2Hz, 1H); MS: m/e=371.88;

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)-4-fluorobenzamide

(Compound 134); ¹H NMR (CDCl₃): 7.74 (m, 2H), 7.47 (t, J=5.9Hz, 1H), 7.29 (m, 4H), 25 7.09 (m, 4H), 4.72 (dd, J=13.6, 6.9Hz, 1H), 4.11 (m, 2H), 3.77 (s, 5H), 3.02 (dd, J=13.8, 6.2Hz, 1H), 2.83 (dd, J=13.8, 7.2Hz, 1H); MS: m/e=371.79;

N-(1S-cyanomethylcarbamoyl-2-(4-methoxybenzylsulfanyl)ethyl]benzamide

(Compound 135); ¹H NMR (DMSO): 8.94 (d, J = 8Hz, 1H), 8.87 (d, J = 6Hz, 1H), 7.87 (d, J = 7Hz, 2H), 7.5 (m, 3H), 7.24 (d, J = 10Hz, 2H), 6.93 (d, J = 10Hz, 2H), 4.80 (dd, J =

4.12Hz, 1H), 4.14 (d, J = 14Hz, 1H), 4.13 (s, 2H), 3.99 (d, J = 14Hz, 1H), 3.74 (s, 3H), 3.16 (dd, J = 12, 14Hz, 1H), 3.07 (dd, J = 14, 4Hz, 1H); MS: m/e = 400.00;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-methylbenzamide

(Compound 136); ¹H NMR (DMSO): 7.7 (t, 1H), 7.65 (d, 2H), 7.25 (d, 2H), 6.65 (d, 1H),
5 4.75 (m, 1H), 4.2 (dd, 1H), 4.03 (dd, 1H), 2.4 (s, 3H), 2-0.8 (m, 13H); MS: m/e 328.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-phenoxybenzamide

(Compound 137); ¹H NMR (CDCl₃): 8.49 (t, J=5.5Hz, 1H), 7.75 (dd, J=10, 8.5Hz, 1H),
7.6-6.9 (m, 9H), 4.84 (m, 1H), 3.95 (m, 2H), 2.0-0.8 (m, 13H); MS: m/e = 405.93;

3-benzoyl-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

10 (Compound 138); ¹H NMR (CDCl₃): 8.19 (t, J=3Hz, 1H), 8.0 (m, 1H), 7.89 (d, J=8.8Hz, 1H), 7.76-7.4 (m, 5H), 6.88 (m, 1H), 4.74 (m, 1H), 4.19 (dd, J=6, 6.3Hz, 1H), 4.08 (dd, J=6, 6.3Hz, 1H), 2.0-0.8 (m, 13H); MS: m/e = 417.95;

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)thiophene-3-carboxamide

(Compound 139);

15 3-acetyl-N-(1R-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

(Compound 140); ¹H NMR: (CDCl₃) 8.33 (t, J=1.5Hz, 1H), 8.08 (dt, J=1.7Hz, J=7.7Hz, 1H), 7.99 (dt, J=1.7Hz, J=7.9Hz, 1H), 7.55 (t, J=7.7Hz, 1H), 7.45 (t, J=6.7Hz, 1H), 6.92 (d, J=7.9Hz, 1H), 4.74 (m, 1H), 4.23-4.05 (m, 2H), 2.63 (s, 3H), 1.90-0.84 (m, 13H); MS: (M⁺+1) 355.8;

20 N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)-4-methoxybenzamide

(Compound 141); ¹H NMR (CDCl₃): 7.81 (t, J=5.7Hz, 1H), 7.70 (dt, J=8.9, 2.2Hz, 2H), 7.20-7.32 (m, J=5H), 7.04 (d, J=7.7Hz, 1H), 6.89 (dt, J=8.9, 2.0Hz, 2H), 4.82 (dd, J=14.1, 6.7Hz, 1H), 4.08 (d, J=5.7Hz, 2H), 3.83 (s, 3H), 3.74 (s, 2H), 3.00 (dd, J=13.9, 6.7Hz, 1H), 2.86 (dd, J=13.9, 6.7Hz, 1H); MS: m/e=383.80;

25 N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)furan-2-carboxamide

(Compound 142); ¹H NMR (CDCl₃): 7.49 (m, 1H), 7.24-7.39 (m, 5H), 7.14 (m, 1H), 7.04 (m, J= 2H), 6.53 (dd, J 3.7, 1.7Hz, 1H), 4.64 (m, 1H), 4.13 (dd, J=5.9, 1.2Hz, 2H), 3.79 (dd, J=16.1, 13.6Hz, 2H), 3.03 (dd, J=14.1, 5.9Hz, 1H), 2.80 (dd, J=14.3 6.9Hz, 1H); MS: m/e=343.84;

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)furan-3-carboxamide

(Compound 143); ¹H NMR: 8.33 (t, J = 5.45 Hz, 1H), 7.16 – 7.28 (m, 5H), 5.41 (d, J = 7.2 Hz, 1H), 4.52 (dd, J = 13.9, 6.7 Hz, 1H), 4.06 (d, J = 5.7 Hz, 2H), 3.68 (s, 2H), 3.10 (s, 3H), 3.05 (m, 1H), 3.00 (s, 3H), 2.80 (m, 1H); MS (320.74);

5 *N*-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)-2-methoxybenzamide

(Compound 144); ¹H NMR (CDCl₃): 8.75 (d, J = 6.9 Hz, 1H), 8.14 (dd, J = 2.0, 7.9 Hz, 1H), 7.50 (m, 1H), 7.20-7.35 (m, 6H), 7.12 (m, 1H), 4.78 (dd, J = 12.6, 6.2 Hz, 1H), 4.19 (dd, J = 12.6, 6.2 Hz, 1H), 4.07 (dd, J = 13.5, 5.4 Hz, 1H), 3.97 (s, 3H), 3.80 (d, J = 3.2 Hz, 2H), 3.08 (dd, J = 14.0, 3.7 Hz, 1H), 2.86 (dd, J = 14.1, 6.7 Hz, 1H); MS: m/e = 383.93;

10 *N*-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)-3-methoxybenzamide

(Compound 145); ¹H NMR (CDCl₃): 7.96 (t, J = 5.7 Hz, 1H), 7.16-7.36 (m, 8H), 7.05 (m, 1H), 4.80 (m, 1H), 4.08 (d, J = 5.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 2H), 2.98 (dd, J = 13.9, 6.4 Hz, 1H), 2.86 (dd, J = 6.9, 3.9 Hz, 1H); MS: m/e = 383.77;

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)morpholine-4-carboxamide

15 (Compound 146); ¹H NMR (CDCl₃): 7.45 (m, 1H), 7.23 (m, 5H), 5.28 (m, 1H), 4.39 (m, 1H), 4.16 (dd, J = 17.6, 5.9 Hz, 1H), 4.06 (dd, J = 11.1, 5.5 Hz, 1H), 3.74 (s, 2H), 3.67 (t, J = 4.9 Hz, 4H), 3.31 (m, 4H), 3.00 (dd, J = 14.1, 6.4 Hz, 1H), 2.77 (dd, J = 13.8, 6.7 Hz, 1H); MS: (362.86);

6-amino-*N*-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)nicotinamide

20 (Compound 147); ¹H NMR (CDCl₃): 8.42 (d, J = 2.5 Hz, 1H), 7.80 (dd, J = 8.7, 2.5 Hz, 1H), 7.18-7.30 (m, 5H), 6.46 (dd, J = 9.4, 0.7 Hz, 1H), 4.64 (t, J = 6.9 Hz, 1H), 4.08 (s, 2H), 3.70 (s, 2H), 2.80 (m, 2H); MS: m/e = 369.4474;

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)-3-pyrid-3-ylacrylamide

25 (Compound 148); ¹H NMR (CDCl₃): 8.72 (d, J = 2.2 Hz, 1H), 8.54 (J = 4.7, 1.5 Hz, 1H), 7.82 (dt, J = 7.9, 2.2 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.18-7.38 (m, 6H), 6.48 (d, J = 15.8 Hz, 1H), 4.61 (m, 1H), 4.10 (s, 2H), 3.73 (s, 2H), 2.80 (m, 2H); MS: m/e = 380.4706;

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)naphthalene-2-carboxamide

(Compound 149); ¹H NMR (CDCl₃): 8.28 (m, 1H), 7.90 (m, 3H), 7.78 (dd, J = 8.4, 1.8 Hz, 1H), 7.57 (m, 2H), 7.17 – 7.38 (m, 6H), 7.13 (J = 7.2 Hz, 1H), 4.77 (m, 1H), 4.14 (d, J =

5.9Hz, 2H), 3.81 (s, 2H), 3.12 (dd, J = 14.1, 5.9Hz, 1H), 2.88 (dd, J = 14.1, 7.2Hz, 1H); MS (403.92);

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)benzofuran-2-carboxamide
(Compound 150); ¹H NMR (DMSO): 7.66 (dt, J = 7.9, 1.2Hz, 1H), 7.16 – 7.54 (m, 9H),
5 4.74 (m, 1H), 4.15 (d, J = 6Hz, 2H), 3.80 (dd, J = 15.3, 13.6Hz, 2H), 3.07 (dd, J =
14.1, 5.9Hz, 1H), 2.87 (dd, J = 14.1, 7.1Hz, 1H); MS (393.83);

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)biphenyl-4-carboxamide
(Compound 151); ¹H NMR (CDCl₃): 7.81 (dt, J = 8.7, 1.5Hz, 2H), 7.66 (m, 2H), 7.59 (m,
2H), 7.26 – 7.49 (m, 7H), 7.02 (d, J = 7.2Hz, 1H), 4.73 (m, 1H), 4.14 (dd, J = 5.9, 1.2Hz,
10 2H), 3.80 (s, 2H), 3.10 (dd, J = 14.0, 7.2Hz, 1H), 2.86 (dd, J = 14.1, 7.2Hz, 1H); MS
(429.99);

N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)benzo[1,3]dioxole-5-carboxamide
(Compound 152); ¹H NMR (CDCl₃): 7.21 – 7.38 (m, 7H), 6.82 (d, J = 8.2Hz, 1H), 6.82
(m, 1H), 4.67 (dd, J = 13.3, 6.9Hz, 1H), 4.11 (dd, J = 5.7, 1.6Hz, 1H), 3.77 (s, 2H), 3.03
15 (dd, J = 14.1, 6.2Hz, 1H), 2.82 (dd, J = 14.1, 6.9Hz, 1H); MS (397.82);

N-(2-*tert*-butylsulfanyl-1*R*-cyanomethylcarbamoylethyl)benzamide (Compound 153);
¹H NMR (DMSO): 8.77 (t, J = 6Hz, 1H), 8.69 (d, J = 9Hz, 1H), 7.89 (d, J = 7Hz, 2H), 7.5
(m, 3H), 4.58 (m, 1H), 4.13 (t, J = 3Hz, 2H), 3.02 (dd, J = 6, 14Hz, 1H), 2.90 (dd, J =
10, 14Hz, 1H), 1.27 (s, 9H); MS: m/e = 319.80;

20 *N*-(1*R*-cyanomethylcarbamoyl-3-phenylsulfanylpropyl)benzamide (Compound 154);
¹H NMR (DMSO): 8.7 (m, 2H), 7.92 (d, J = 7Hz, 2H), 7.53 (m, 3H), 7.3 (m, 4H), 7.2 (m,
1H), 4.6 (q, J = 7Hz, 1H), 4.13 (d, J = 6Hz, 2H), 3.0 (m, 2H), 2.05 (m, 2H); MS: m/e =
353.83;

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-methylthiophene-2-carboxamide
25 (Compound 155); ¹H NMR: (CDCl₃) 7.75 (t, J=6Hz, 1H), 7.32 (d, J=5Hz, 1H), 6.90 (d,
J=5Hz, 1H), 6.30 (d, J=7.9Hz, 1H), 4.72 (m, 1H), 4.19 (dd, J=5.7Hz, J=17.5Hz, 1H), 4.05
(dd, J=5.7Hz, J=17.3Hz, 1H), 2.51 (s, 3H), 1.85-0.85 (m, 13H); MS: (M⁺+1) 333.9;

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)-5-methylthiophene-2-carboxamide
(Compound 156); ¹H NMR: (CDCl₃) 8.14 (t, J=5.7Hz, 1H), 7.39 (d, J=3.7Hz, 1H), 6.93

(d, J=7.9Hz, 1H), 6.72 (dd, J=1Hz, J=3.7Hz, 1H), 4.74 (m, 1H), 4.17 (dd, J=5.9Hz, J=17Hz, 1H), 3.97 (dd, J=5.5Hz, J=17.1Hz, 1H), 2.50 (s, 3H), 1.80-0.82 (m, 13H); MS: (M⁺+1) 333.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-chlorothiophene-2-carboxamide
5 (Compound 157); ¹H NMR: (CDCl₃) 7.52 (d, J=5.2Hz, 1H), 7.43 (t, J=5.7Hz, 1H), 7.32 (d, J=7.4Hz, 1H), 7.01 (d, J=5.2Hz, 1H), 4.68 (m, 1H), 4.23 (dd, J=5.9Hz, J=17.5Hz, 1H), 4.08 (dd, J=6Hz, J=17.3Hz, 1H), 1.90-0.85 (m, 13H); MS: (M⁺+1) 353.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-chlorobenzo[b]thiophene-2-carboxamide
10 (Compound 158); ¹H NMR: (CDCl₃) 7.90-7.78 (m, 3H), 7.65 (d, J=7.9Hz, 1H), 7.51-7.42 (m, 2H), 4.86 (q, J=8Hz, 1H), 4.28 (dd, J=5.9Hz, J=17.3Hz, 1H), 4.12 (dd, J=5.7Hz, J=17.3Hz, 1H), 1.90-0.85 (m, 13H); MS: (M⁺+1) 403.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-5-chlorothiophene-2-carboxamide
(Compound 159); ¹H NMR: (CDCl₃) 8.18 (t, J=5.7Hz, 1H), 7.62 (d, J=7.9Hz, 1H), 7.40 (d, J=4Hz, 1H), 6.88 (d, J=4Hz, 1H), 4.70 (q, J=7.7Hz, 1H), 4.14 (dd, J=5.7Hz, J=17Hz, 1H), 4.05 (dd, J=6Hz, J=17Hz, 1H), 1.80-0.84 (m, 13H); MS: (M⁺+1) 353.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-bromothiophene-2-carboxamide
(Compound 160); ¹H NMR (CDCl₃): 7.55-7.39 (m, 3H), 7.07 (d, J=5.5Hz, 1H), 4.68 (m, 1H), 4.25 (dt, 1H), 4.08 (dt, 1H), 2.0-0.8 (m, 13H); MS: m/e =399.74;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-5-bromothiophene-2-carboxamide
20 (Compound 161); ¹H NMR (CDCl₃): 8.18 (t, J=5.4Hz, 1H), 7.62 (d, J=3.5Hz, 1H), 7.37 (d, J=4.0Hz, 1H), 7.04 (d, J=4.0Hz, 1H), 4.70 (dd, J=7.2, 18.7Hz, 1H), 4.15 (dd, J=5.7, 17.8Hz, 1H), 4.05 (dd, J=5.7, 17.8, 1H), 1.5-1.8 (m, 7H), 0.8-1.50 (m, 6H); MS: m/e (+1) 399.83;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzo[b]thiophene-2-carboxamide
25 (Compound 162); NMR (MeOH): 8.06 (s, 1H), 7.91 (m, 2H), 7.43 (m, 2H), 4.64 (dd, J=6.7, 8.7Hz, 1H), 4.21 (d, J=17.3Hz, 1H), 4.13 (d, J=17.3Hz, 1H), 1.61-1.90 (m, 8H), 0.89-1.55 (m, 4H); MS: m/e=369.78;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-ethoxybenzamide
(Compound 163); ¹H NMR (MeOH): 8.50 (d, J=7.4Hz, 1H), 7.3-7.43 (m, 3H), 7.07 (d,

J=8.2Hz, 1H), 4.64 (dd, J=7.7, 19.2Hz, 2H), 4.15 (d, J=4.2Hz, 2H), 4.09 (d, J=6.9Hz, 1H), 4.04 (d, J=6.9Hz, 1H), 1.35 (t, J=7.0, 3H), 0.9-1.9 (m, 13H); MS: m/e (+1) 357.94;

tert-butyl 3-(1S-cyanomethylcarbamoyl-3-methylbutylcarbamoyl)phenylcarbamate
(Compound 164);

5 tert-butyl 3-(2-benzylsulfanyl-

1R-cyanomethylcarbamoyl-ethylcarbamoyl)phenylcarbamate (Compound 165);

N-(1-cyanomethylcarbamoyl-3-phenoxypropyl)benzamide (Compound 166); ¹H NMR (DMSO): 8.71 (m, = 2H), 7.90 (d, J = 14Hz, 2H), 7.5 (m, 3H), 7.25 (m, 2H), 6.9 (m, 3H), 4.65 (m, 1H), 4.14 (d, J = 6Hz, 2H), 4.04 (m, 2H), 2.25 (m, 2H); MS: m/e = 337.84;

10 tert-butyl 1S-cyanomethylcarbamoyl-2-(4-nitrophenyl)ethylcarbamate

(Compound 167);

N-(1-cyanomethylcarbamoyl-5-fluoropentyl)benzamide (Compound 168); ¹H NMR (DMSO): 8.69 (t, J = 6Hz, 1H), 8.57 (d, J = 8Hz, 1H), 7.90 (d, J = 7Hz, 2H), 7.5 (m, 3H), 4.42 (dt, J = 52.6Hz, 2H), 4.43 (m, 1H), 4.13 (s, 2H), 1.83 – 1.3 (m, 6H); MS: m/e =

15 291.84;

tert-butyl 3-(1S-cyanomethylcarbamoylpentylcarbamoyl)phenylcarbamate
(Compound 169);

tert-butyl 3-cyanomethylcarbamoylmethylcarbamoylphenylcarbamate
(Compound 170);

20 N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl-ethyl)quinoline-3-carboxamide

(Compound 171); ¹H NMR (DMSO): 9.30 (d, J = 2.5Hz, 1H), 8.58 (d, J = 2.5Hz, 1H), 8.16 (d, J = 8.7Hz, 1H), 7.90 (d, J = 9.2Hz, 1H), 7.83 (td, J = 8.7, 1.5Hz, 1H), 7.63 (td, J = 6.9, 1.2Hz, 1H), 7.17 – 7.42 (m, 5H), 4.77 (dd, J = 11.8, 7.2Hz, 1H), 3.81 (s, 2H), 3.12 (dd, J = 13.9, 6.2Hz, 1H), 2.90 (dd, J = 14.0, 7.4Hz, 1H); MS (404.77);

25 tert-butyl 3-(1S-cyanomethylcarbamoyl-

2-cyclohexylethylcarbamoylbenzyl)carbamate (Compound 172); ¹H NMR (CDCl₃): 8.15 (bt, J=5.45Hz, 1H), 7.63 (d, J=8.1Hz, 2H), 7.43 (d, J=7.7Hz, 1H), 5.18 (s, 1H), 4.81 (dd, J=8.4, 18.8Hz, 1H), 4.25 (d, J=5.2Hz, 2H), 4.15 (dd, J=5.9, 17.1Hz, 1H), 3.98 (dd, J=5.9, 17.1Hz, 1H), 1.45 (s, 9H), 0.8-1.9 (m, 13H); MS: m/e (+1) 357.94;

3-acetylamino-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

(Compound 173); ¹H NMR (CDCl₃): 8.43 (s, 1H), 8.32 (s, 1H), 7.94 (3, J=7.92Hz, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.38 (d, J=7.9Hz, 1H), 4.83 (dd, J=7.4, 15.3Hz, 1H), 4.23 (dd, J=5.7, 17.3Hz, 1H), 4.06 (dd, J=5.7, 17.3Hz, 1H), 2.14 (s, 3H), 0.95-1.90 (m, 13H); MS:

5 m/e=370.85;

2S-[2-(4-butoxyphenyl)acetylamino]-N-cyanomethyl-3-cyclohexylpropionamide

(Compound 174); NMR (MeOH): 7.19 (d, J=8.9Hz, 2H), 6.84 (d, J=8.9Hz, 2H), 4.38 (dd, J=5.9, 9.4Hz, 1H), 4.12 (d, J=2.2Hz, 2H), 3.94 (t, J=6.4Hz, 2H), 3.60 (d, J=14.1Hz, 1H), 3.46 (d, J=14.1Hz, 1H), 1.40-1.78 (m, 4H), 1.05-1.3 (m, 3H), 0.95 (t, J=7.4Hz, 3H); MS:

10 m/e=399.95;

N-[1S-cyanomethylcarbamoyl-2-(4-nitrophenyl)ethyl]morpholine-4-carboxamide

(Compound 175);

N-cyanomethyl-3-cyclohexyl-2S-(3-naphth-2-ylureido)propionamide

(Compound 176);

15 N-cyanomethyl-3-cyclohexyl-2S-(3-hexylureido)propionamide (Compound 177);

2S-(3-allylureido)-N-cyanomethyl-3-cyclohexylpropionamide (Compound 178);

N-cyanomethyl-3-cyclohexyl-2S-[3-(2,2,4-trimethylpentyl)ureido]propionamide

(Compound 179);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)quinoline-2-carboxamide

20 (Compound 180); ¹H NMR (CDCl₃): 8.90 (d, J = 7.8Hz, 1H), 8.35 (m, 1H), 8.22 (m, 3H), 7.89 (m, 1H), 7.81 (td, J = 7.2, 1.7Hz, 1H), 7.66 (td, J = 6.9, 1.0Hz, 1H), 7.37 (m, 2H), 7.14 – 7.32 (m, 3H), 4.77 (m, 1H), 4.16 (m, 2H), 3.82 (s, 2H), 3.11 (dd, J = 14.1, 6.2Hz, 1H), 3.00 (dd, J = 14.1, 6.9Hz, 1H); MS (404.8);

3-benzylsulfanyl-N-cyanomethyl-2R-(3,3-dimethylureido)propionamide

25 (Compound 181);

3-benzoyl-N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)benzamide

(Compound 182); ¹H NMR (CDCl₃): 8.19 (t, J = 1.6Hz, 1H), 7.96 (m, 2H), 7.78 (m, 2H), 7.61 (m, 2H), 7.51 (m, 2H), 7.23 – 7.37 (m, 5H), 6.99 (d, J = 6.2Hz, 2H), 4.64 (m, 1H), 4.13 (dd, J = 5.9, 1.0Hz, 2H), 3.80 (d, J = 2.5Hz, 2H), 3.09 (dd, J = 14.1, 6.9Hz, 2H), 2.81

(dd, J = 14.1, 7.7 Hz, 1H); MS (457.81);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-

5-pyrid-2-ylthiophene-2-carboxamide (Compound 183); ¹H NMR (CDCl₃): 8.55 (d, J=4.95 Hz, 1H), 8.05 (s, J=5.4 Hz, 1H), 7.67-7.73 (m, 2H), 7.62 (d, J=4.0 Hz, 1H), 7.54 (d, J=4.0 Hz, 1H), 7.21 (m, 1H), 7.11 (d, J=7.9 Hz, 1H), 4.77 (dd, J=8.4, 14.3 Hz, 1H), 4.21 (dd, J=5.7, 17.3 Hz, 1H), 4.06 (dd, J=5.7, 17.3 Hz, 1H), 0.8-2.0 (m, 13H); MS: m/e=396.8;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-

4-methoxythiophene-3-carboxamide (Compound 184); ¹H NMR (CDCl₃): 8.04 (d, J=3.7 Hz, 2H), 7.74 (d, J=7.4 Hz, 1H), 6.35 (d, J=3.4 Hz, 1H), 4.68 (dd, J=8.4, 13.9 Hz, 1H), 4.18 (dd, J=6.2, 17.3 Hz, 1H), 4.12 (dd, J=6.2, 17.13 Hz, 1H), 3.91 (s, 3H), 0.8-1.9 (m, 13H); MS: m/e=349.78;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-

3-(3-methylbenzoyl)aminobenzamide (Compound 185); ¹H NMR (CDCl₃): 8.47 (s, 1H), 8.30 (t, J=5.4 Hz, 1H), 7.98 (d, J=8.2 Hz, 1H), 7.84 (s, 1H), 7.68 (m, 2H), 7.2-7.48 (m, 4H), 4.84 (dd, J=8.2, 14.6 Hz, 1H), 4.26 (dd, J=6.2, 17.3 Hz, 1H), 4.02 (dd, J=6.2, 17.3 Hz, 1H), 2.35 (s, 3H), 0.8-1.9 (m, 14H); MS: m/e=446.90;

2S-(3-phenylsulfonylureido)-N-cyanomethyl-3-cyclohexylpropionamide

(Compound 186);

4-benzoyl-N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl)benzamide

(Compound 187); ¹H NMR (CDCl₃): 8.348 (1H), 8.11 (d, J = 6.6 Hz, 1H), 7.95 (d, J = 6.2 Hz, 1H), 7.56 (m, 1H), 7.14 - 7.54 (m, 7H), 4.73 (m, 1H), 4.16 (d, J = 5.9 Hz, 2H), 3.80 (m, 2H), 3.08 (dd, J = 13.9, 7.3 Hz, 1H), 2.87 (dd, J = 13.9, 6.2 Hz, 1H), 2.64 (s, 3H); MS (459.86);

N-[2-(4-aminophenyl)-1S-cyanomethylcarbamoyl]morpholine-4-carboxamide

(Compound 188);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl)nicotinamide (Compound 189);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl)isonicotinamide

(Compound 190);

2S-(3-tert-butylureido)-N-cyanomethyl-3-cyclohexylpropionamide

(Compound 191);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-methylpentanamide

(Compound 192); ¹H NMR (CDCl₃): 8.25 (t, J=5.7Hz, 1H), 6.60 (d, J=8.2Hz, 1H), 4.60 (dd, J=8.7, 14.6Hz, 1H), 4.12 (dd, J=5.7, 14.8Hz, 1H), 4.04 (dd, J=5.7, 14.8Hz, 1H), 2.20 (t, J=8.2Hz, 2H), 0.85 (d, J=6.5, 6H), 1.1-1.8 (m, 16H); MS: m/e (+1) 307.92;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)cyclopent-1-enecarboxamide

(Compound 193); ¹H NMR (CDCl₃): 7.79 (t, J=5.9Hz, 1H), 6.49 (m, 1H), 6.08 (d, J=7.9Hz, 1H), 4.58 (dd, J=8.4, 14.6Hz, 1H), 4.17 (dd, J=5.9, 17.3Hz, 1H), 4.04 (dd, J=5.9, 17.3Hz, 1H), 2.52 (m, 4H), 2.0 (m, 2H), 1.68 (m, 8H), 0.8-1.4 (m, 5H); MS: m/e (+1) 303.82;

tert-butyl 2-benzylsulfanyl-1R-cyanomethylcarbamoylethylcarbamate

(Compound 194);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-1H-imidazole-4-carboxamide

(Compound 195); ¹H NMR (DMSO): 8.10 (s, 1H), 7.60 (m, 4H), 4.62 (m, 1H), 4.10 (d, J=7.2Hz, 2H), 0.8-1.90 (m, 13H); MS: m/e (+1) 303.79;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-cyclopentanecarboxamide

(Compound 196); ¹H NMR (DMSO): 7.88 (t, J=5.45Hz, 1H), 6.15 (d, J=8.17Hz, 1H), 4.55 (dd, J=8.7, 14.6Hz, 1H), 4.16 (dd, J=5.7, 17.3Hz, 1H), 4.06 (dd, J=5.7, 17.3Hz, 1H), 2.65 (m, 1H), 0.8-1.95 (m, 21H); MS: m/e (+1) 305.91;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)cyclohex-1-enecarboxamide

(Compound 197); ¹H NMR (DMSO): 7.65 (t, J=5.2Hz, 1H), 6.69 (m, 1H), 6.02 (d, J=7.7Hz, 1H), 4.56 (dd, J=8.7, 14.1Hz, 1H), 4.17 (dd, J=5.9, 17.3Hz, 1H), 4.05 (dd, J=5.9, 17.3Hz, 1H), 2.19 (m, 4H), 1.48-1.85 (m, 13H), 0.8-1.4 (m, 4H); MS: m/e (+1) 317.86;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-5-methylsulfanyltiophene-

2-carboxamide (Compound 198); ¹H NMR (CDCl₃): 8.12 (t, J=5.4Hz, 1H), 7.42 (d, J=4.0Hz, 1H), 7.18 (d, J=7.7Hz, 1H), 6.9 (d, J=4.0Hz, 1H), 4.73 (dd, J=8.2, 14.6Hz, 1H), 4.18 (dd, J=8.2, 14.6Hz, 1H), 2.55 (s, 3H), 1.75 (m, 8H), 0.8-1.5 (m, 6H); MS: m/e (+1) 365.77;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)isobutyramide (Compound 199); ¹H

NMR (CDCl₃): 7.88 (t, J=5.7Hz, 1H), 6.14 (d, J=7.9Hz, 1H), 4.55 (dd, J=8.7, 14.6Hz, 1H), 4.15 (dd, J=5.7, 15.6Hz, 1H), 4.06 (dd, J=5.7, 15.6Hz, 1H), 2.40 (m, 1H), 1.57-1.80 (m, 8H), 0.8-1.40 (m, 11H); MS: m/e (+1) 279.89;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)furan-2-carboxamide

- 5 (Compound 200); ¹H NMR (CDCl₃): 7.45 (m, 2H), 7.14 (d, J=3.5Hz, 1H), 6.67 (d, J=8.2Hz, 1H), 6.51 (m, 2H), 4.66 (dd, J=8.9, 14.1Hz, 1H), 4.20 (dd, J=5.9, 17.6Hz, 1H), 4.06 (dd, J=5.9, 17.6, 1H), 1.5-1.9 (m, 7H), 0.8-1.40 (m, 6H); MS: m/e (+1) 303.83;

N-cyanomethyl-3-cyclohexyl-2S-(3-cyclohexylureido)propionamide

(Compound 201);

- 10 N-cyanomethyl-3-cyclohexyl-2S-(3-phenylureido)propionamide (Compound 202);
3-acetylamino-N-(1S-cyanomethylcarbamoylpentyl)benzamide (Compound 203);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)furan-3-carboxamide

- (Compound 204); ¹H NMR (CDCl₃): 8.5 (t, J=6Hz, 1H), 7.95 (s, 1H), 7.8 (d, J=6Hz, 1H), 7.4 (s, 1H), 6.65 (s, 1H), 4.70 (m, 1H), 4.15 (dd, J=6,6Hz, 1H), 3.95 (dd, J=6,6Hz, 1H),
15 2.0-0.8 (m, 13H); MS: m/e =303.70;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-6-hydroxynicotinamide

(Compound 205); ¹H NMR (DMSO): 12.1 (s, 1H), 8.8 (t, J=5.7Hz, 1H), 8.4 (d, J=7.5Hz, 1H), 8.1 (d, J=2.1Hz, 1H), 7.9 (dd, J=3,10Hz, 1H), 6.43 (d, J=10Hz, 1H), 4.5-4.2 (m, 1H), 4.18 (d, J=6Hz, 1H), 1.8-0.8 (m, 13H); MS: m/e =330.82;

- 20 N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzofuran-2-carboxamide

(Compound 206); ¹H NMR (CDCl₃): 7.95 (t, J=6Hz, 1H), 7.8-7.2 (m, 6H), 4.95 (m, 1H), 4.30 (dd, J=6,6Hz, 1H), 4.10 (dd, J=6,6Hz, 1H), 2.0-0.8 (m, 13H); MS: m/e =303.70;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)quinoline-3-carboxamide

- (Compound 207); ¹H NMR (DMSO): 9.2 (s, 1H), 8.8 (s, 1H), 8.0 (d, J=6Hz, 2H), 7.8
25 (t, J=6Hz, 1H), 7.65 (t, J=6Hz, 1H), 4.2 (m, 2H), 2.0-0.8 (m, 15H); MS: m/e =364.86;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-4-hydroxy-3-nitrobenzamide

(Compound 208); ¹H NMR (CDCl₃): 10.7 (s, 1H), 8.3 (s, 2H), 7.9 (d, J=6Hz, 1H), 7.1 (d, J=6Hz, 1H), 4.9 (m, 1H), 4.3 (m, 2H), 2.2-0.8 (m, 13H); MS: m/e =374.83;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-nitrobenzamide

(Compound 209); ¹H NMR (DMSO): 8.8-8.2 (m, 4H), 8.1 (d, J=6.8Hz, 1H), 7.5 (t, J=6.8Hz, 1H), 4.9 (m, 1H), 4.45 (dd, J=6,6, 1H), 4.25 (dd, J=6,6, 1H), 2.0-0.8 (m, 13H); MS:m/e =358.75;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-methylbutyramide

5 (Compound 210); ¹H NMR (CDCl₃): 7.9 (t, J=3, 6Hz, 1H), 6.3 (d, J=6Hz, 1H), 4.6 (m, 1H), 4.1 (m, 2H), 2.3-0.8 (m, 22H); MS:m/e =293.73;

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)-1H-indole-5-carboxamide

(Compound 211); ¹H NMR (CD₃OD): 8.12 (s, 1H), 7.61 (d, J = 7.7Hz, 1H), 7.39 (d, J = 8.4Hz, 1H), 7.28 (m, 6H), 7.22 (m, 1H), 7.16 (m, 1H), 6.52 (m, 1H), 4.73 (m, 1H), 4.14 (s, 10 2H), 3.75 (s, 1H), 2.97 (m, 1H), 2.79 (m, 1H); MS (393.2);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)-3-phenoxybenzamide

(Compound 212); ¹H NMR (CDCl₃): 7.55 (m, 1H), 7.45 (m, 1H), 7.39 (m, 1H), 7.26 (m, 6H), 7.12 (m, 3H), 6.97 (m, 2H), 4.67 (m, 1H), 4.11 (d, J = 3.7Hz, 2H), 3.72 (d, J = 3.7Hz, 2H), 2.93 (m, 1H), 2.73 (m, 1H); MS (446.4);

15 tert-butyl 3-(2-benzylsulfanyl-

1R-cyanomethylcarbamoylethylcarbamoyl)benzylcarbamate (Compound 213); ¹H NMR (CDCl₃): 7.69 (s, 1H), 7.62 (m, 1H), 7.48 (d, J = 7.2Hz, 1H), 7.41 (d, J = 7.8Hz, 1H), 7.28 (m, 4H), 7.12 (J = 7.2Hz, 1H), 4.74 (dd, J = 13.5,6.9Hz, 1H), 4.33 (s, 2H), 4.13 (d, J = 5.4Hz, 2H), 3.77 (s, 2H), 3.01 (dd, J = 14.4,6.3Hz, 1H), 2.85 (dd, J = 13.8,7.2Hz, 1H), 1.45 20 (s, 9H); MS (483);

3-acetyl-N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)benzamide

(Compound 214); ¹H NMR (CDCl₃): 8.348 (1H), 8.11 (d, J = 6.6Hz, 1H), 7.95 (d, J = 6.2Hz, 1H), 7.56 (m, 1H), 7.14 – 7.54 (m, 7H), 4.73 (m, 1H), 4.16 (d, J = 5.9Hz, 2H), 3.80 (m, 2H), 3.08 (dd, J = 13.9,7.3Hz, 1H), 2.87 (dd, J = 13.9,6.2Hz, 1H), 2.64 (s, 3H); MS 25 (396.0);

3-(3-methylbenzoylamino-N-(2-benzylsulfanyl-

1R-cyanomethylcarbamoylethyl)benzamide (Compound 215); ¹H NMR (CDCl₃): 8.12 (s, 1H), 7.95 (m, 2H), 7.70 (s, 1H), 7.66 (m, 1H), 7.20 – 7.47 (m, 8H), 7.12 (d, J = 6.9Hz, 1H), 4.74 (m, 1H), 4.16 (d, J = 5.7Hz, 2H), 3.77 (s, 2H), 3.01 (dd, J = 13.7,5.9Hz, 1H),

2.86 (dd, $J = 13.8, 6.8$ Hz, 1H), 2.42 (s, 3H); MS: (487.4);

N-[(cyanomethylcarbamoyl)(propoxy)methyl]benzamide (Compound 216); ^1H NMR (DMSO): 9.25 (d, $J = 10$ Hz, 1H), 8.65 (t, $J = 6$ Hz, 1H), 7.92 (d, $J = 7$ Hz, 2H), 7.5 (m, 3H), 5.60 (d, $J = 10$ Hz, 1H), 4.18 (m, 2H), 3.51 (m, 2H), 1.56 (h, $J = 8$ Hz, 2H), 0.88 (t, $J = 8$ Hz, 3H);

N-(3-benzylsulfanyl-1*R*-cyanomethylcarbamoylpropyl)benzamide (Compound 217); ^1H NMR (DMSO): 8.69 (t, $J = 6$ Hz, 1H), 8.63 (d, $J = 8$ Hz, 1H), 7.90 (d, $J = 9$ Hz, 2H), 7.5 (m, 3H), 7.2 (m, 5H), 4.54 (m, 1H), 4.13 (d, $J = 6$ Hz, 2H), 3.73 (s, 2H), 2.46 (m, 2H), 2.02 (m, 2H); MS: $m/e = 367.81$;

N-[(cyanomethylcarbamoyl)(cyclohexyloxy)methyl]benzamide (Compound 218); ^1H NMR (DMSO): 9.26 (d, $J = 9$ Hz, 1H), 8.55 (t, $J = 6$ Hz, 1H), 7.92 (d, $J = 7$ Hz, 2H), 7.51 (m, 3H), 5.72 (d, $J = 10$ Hz, 1H), 4.17 (m, 2H), 3.56 (m, 1H), 1.95 (m, 3H), 1.75 (m, 3H), 1.3 (m, 6H); MS: $m/e = 315.8$;

N-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)succinamic acid (Compound 219); ^1H NMR (CDCl_3): 4.38 (m, 1H), 4.05 (s, 2H), 2.45 (d, $J = 6.3$ Hz, 2H), 2.58 (d, $J = 6.3$ Hz, 2H), 0.8-1.9 (m, 15H); MS: $m/e (+1) 309.72$;

3-[3-(2-chloro-6-methylphenyl)ureido]-*N*-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide (Compound 220);

tert-butyl 4-(1*S*-cyanomethylcarbamoyl-2-cyclohexylethylcarbamoyl)phenylcarbamate (Compound 221);

N-(1*S*-cyanomethylcarbamoyl-2-pyrid-4-ylethyl)benzamide (Compound 222); ^1H NMR: (CDCl_3) 8.36 (d, $J = 6$ Hz, 2H), 7.80 (d, $J = 6.5$ Hz, 1H), 7.66 (d, $J = 7.3$ Hz, 2H), 7.47-7.32 (m, 4H), 7.14 (d, $J = 6$ Hz, 2H), 4.79 (m, 1H), 4.06 (d, $J = 17$ Hz, 1H), 3.94 (d, $J = 17$ Hz, 1H), 3.15 (dd, $J = 6.6$ Hz, $J = 13.6$ Hz, 1H), 3.01 (dd, $J = 7.5$ Hz, $J = 14$ Hz, 1H); MS: ($M^+ + 1$) 309;

N-(1*S*-cyanomethylcarbamoyl-2-(4-oxocyclohexyl)ethyl)benzamide (Compound 223); ^1H NMR: (CDCl_3) 7.93 (m, 1H), 7.81 (d, $J = 7$ Hz, 2H), 7.59-7.44 (m, 3H), 7.13 (t, $J = 8$ Hz, 1H), 4.85 (m, 1H), 4.23-4.08 (m, 2H), 2.38-1.25 (m, 11H); MS: ($M^+ + 1$) 328;

N-[1S-cyanomethylcarbamoyl-2-(4,4-difluorocyclohexyl)ethyl]benzamide

(Compound 224); ¹H NMR: (CDCl₃) 8.04 (m, 1H), 7.80 (d, J=7.4Hz, 2H), 7.58-7.42 (m, 3H), 7.20 (d, J=6Hz, 1H), 4.84 (m, 1H), 4.21-4.03 (m, 2H), 2.20-1.23 (m, 11H); MS: (M⁺+1) 350;

5 N-[1S-cyanomethylcarbamoyl-2-cyclohexylethyl]thiomorpholine-4-carboxamide

(Compound 225); ¹H NMR (DMSO): 7.75 (m, 1H), 4.99 (m, 1H), 4.37 (m, 1H), 4.12 (m, 1H), 3.7 (m, 4H), 2.61 (m, 4H), 2-0.8 (m, 13H); MS: m/e 339.4;

4-(1S-cyanomethylcarbamoyl-2-cyclohexylethylcarbamoyl)butyric acid

(Compound 226);

10 N-[(cyanomethylcarbamoyl)(phenethyloxy)methyl]benzamide (Compound 227); ¹H

NMR (DMSO): 9.30 (d, J = 9Hz, 1H), 8.69 (t, J = 7Hz, 1H), 7.90 (d, J = 8Hz, 2H), 7.51 (m, 3H), 7.2 (m, 5H), 5.66 (m, 1H), 4.19 (m, 2H), 3.77 (m, 2H), 2.92 (m, 2H); MS: m/e = 337.94;

4-amino-N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)benzamide

15 (Compound 228);

tert-butyl 4-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethylcarbamoyl)piperazine-

1-carboxylate (Compound 229); ¹H NMR (CDCl₃): 7.46 (t, J = 5.7Hz, 1H), 7.31 (m, 5H), 5.27 (d, J = 6.9Hz, 1H), 4.38 (dd, J = 13.4, 6.7Hz, 1H), 4.15 (dd, J = 17.3, 5.9Hz, 1H), 4.06 (dd, J = 17.3, 9.9Hz, 1H), 3.73 (s, 2H), 3.42 (t, J = 4.9Hz, 4H), 3.31 (t, J = 4.9Hz, 4H), 2.97 (dd, J = 14.1, 6.7Hz, 1H), 2.77 (dd, J = 13.9, 6.7Hz, 1H), 1.46 (s, 9H); MS (462.4);

20 N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)-4-fur-2-ylcarbonylpiperazine-

1-carboxamide (Compound 230); ¹H NMR (CDCl₃): 7.59 (t, J = 5.7Hz, 1H), 7.50 (dd, J = 2.2, 1.0Hz, 1H), 7.30 (m, 5H), 7.05 (dd, J = 2.4, 0.7Hz, 1H), 6.50 (dd, J = 6.9, 1.7Hz, 1H), 5.42 (d, J = 6.9Hz, 1H), 4.42 (dd, J = 13.3, 6.7Hz, 1H), 4.15 (dd, J = 11.6, 5.9Hz, 1H), 4.06 (dd, J = 16.2, 7.2Hz, 1H), 3.73 (s, 4H), 3.45 (m, 4H), 3.38 (m, 4H), 2.95 (dd, J = 13.9, 6.4Hz, 1H), 2.78 (dd, J = 13.9, 6.7Hz, 1H); MS (456.2);

ethyl 4-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethylcarbamoyl)piperazine-

1-carboxylate (Compound 231); ¹H NMR (CDCl₃): 7.58 (t, J = 5.7Hz, 1H), 7.30 (m, 5H), 5.35 (d, J = 6.9Hz, 1H), 4.41 (dd, J = 13.3, 6.7Hz, 1H), 4.15 (q, J = 7.1Hz, 2H), 4.10 (t, J =

5.9Hz, 2H), 3.72 (s, 2H), 3.47 (t, J = 4.9Hz, 4H), 3.34 (t, J = 3.7Hz, 4H), 2.93 (dd, J = 13.8, 6.4Hz, 1H), 2.76 (dd, J = 13.8, 6.9Hz, 1H), 1.26 (t, J = 7.1Hz, 3H); MS (434.4);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl-ethyl)-4-hydroxybenzamide
(Compound 232);

5 N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl-ethyl)-3-hydroxybenzamide
(Compound 233);

N-[2-(1-acetylpiperidin-4-yl)-1S-cyanomethylcarbamoyl-ethyl]benzamide
(Compound 234); MS: (M⁺+Na) 379;

N-[(cyanomethylcarbamoyl)(phenylamino)methyl]benzamide (Compound 235); ¹H
10 NMR (DMSO): 9.02 (d, J = 9Hz, 1H), 8.91 (t, J = 6Hz, 1H), 7.86 (d, J = 10Hz, 2H), 7.5 (m, 3H), 7.11 (t, J = 9Hz, 2H), 6.78 (d, J = 8Hz, 2H), 6.65 (t, J = 8Hz, 1H), 6.08 (d, J = 9Hz, 1H), 5.87 (m, 1H), 4.20 (t, J = 3Hz, 2H); MS: m/e = 308.99;

N-[1S-cyanomethylcarbamoyl-2-(4-methylenecyclohexyl)ethyl]benzamide
(Compound 236); ¹H NMR: (CDCl₃) 7.81-7.75 (m, 3H), 7.58-7.43 (m, 3H), 6.88 (d,
15 J=8Hz, 1H), 4.80 (m, 1H), 4.59 (s, 2H), 4.20 (dd, J=6Hz, J=17Hz, 1H), 4.08 (dd, J=5.5Hz, J=17Hz, 1H), 2.30-1.48 (m, 9H), 1.15-0.96 (m, 2H); MS: (M⁺+Na) 348;

N-[1S-cyanomethylcarbamoyl-2-(4-ethylidenecyclohexyl)ethyl]benzamide
(Compound 237); ¹H NMR: (CDCl₃) 7.87 (t, J=6Hz, 1H), 7.80 (d, J=7Hz, 2H), 7.58-7.43
(m, 3H), 6.94 (d, J=8Hz, 1H), 5.12 (q, J=6.5Hz, 1H), 4.80 (m, 1H), 4.20 (dd, J=6Hz,
20 J=17Hz, 1H), 4.08 (dd, J=5.5Hz, J=17Hz, 1H), 2.55 (m, 1H), 2.17-1.50 (m, 8H), 1.53 (d, J=6.5Hz, 3H), 1.10-0.91 (m, 2H); MS: (M⁺+Na) 362;

N-[1S-cyanomethylcarbamoyl-2-(4-propylidenecyclohexyl)ethyl]benzamide
(Compound 238); ¹H NMR: (CDCl₃) 8.15 (m, 1H), 7.81 (d, J=8Hz, 2H), 7.56-7.41 (m,
3H), 7.22 (d, J=7Hz, 1H), 5.05 (t, J=7.2Hz, 1H), 4.84 (q, J=7Hz, 1H), 4.18 (dd, J=6Hz,
25 J=17Hz, 1H), 4.05 (dd, J=5.5Hz, J=17Hz, 1H), 2.48 (m, 2H), 2.11-1.47 (m, 9H), 1.03-0.90 (m, 2H), 0.90 (t, J=7.7Hz, 3H); MS: (M⁺+Na) 376;

N-[1S-cyanomethylcarbamoyl-2-(1-ethylpiperidin-4-yl)ethyl]benzamide
(Compound 239); ¹H NMR: (DMSO) 8.68 (t, J=6Hz, 1H), 8.56 (d, J=7Hz, 1H), 7.87 (d,
J=7Hz, 2H), 7.54-7.42 (m, 3H), 4.50 (m, 1H), 4.10 (m, 2H), 2.77 (m, 2H), 2.24 (m, 2H),

1.79-1.05 (m, 9H), 0.93 (t, J=7Hz, 3H); MS: (M⁺+1) 343;

4-[2-benzoylamino-2S-cyanomethylcarbamoyl-ethyl]-1-methylcyclohexyl
trifluoroacetate (Compound 240); ¹H NMR: (CDCl₃) 8.25 (t, J=5Hz, 1H), 7.80 (d, J=7Hz,
2H), 7.58-7.39 (m, 4H), 4.86 (q, J=7.5Hz, 1H), 4.16 (dd, J=5.5Hz, J=17Hz, 1H), 4.04 (dd,
5 J=5.5Hz, J=17Hz, 1H), 2.28 (m, 2H), 1.84-1.07 (m, 9H), 1.51 (s, 3H); MS: (M⁺+1) 440;

N-(2-tert-butyl-disulfanyl-1R-cyanomethylcarbamoyl-ethyl)benzamide
(Compound 241); ¹H NMR (CDCl₃): 7.83 (m, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 7.43 (m,
2H), 7.16 (m, 1H), 5.00 (m, 1H), 4.19 (m, 2H), 3.33 (m, 1H), 3.27 (m, 1H), 1.34 (s, 9H);

N-[1S-cyanomethylcarbamoyl-2-(4-hydroxycyclohexyl)ethyl]benzamide
10 (Compound 242); ¹H NMR: (CDCl₃+10% CD₃OD) 7.75 (d, J=7Hz, 2H), 7.54-7.35 (m,
3H), 4.60 (m, 1H), 4.14 (d, J=17.5Hz, 1H), 4.00 (d, J=17.3Hz, 1H), 3.44 (m, 1H), 1.91-
1.60 (m, 6H), 1.28-0.90 (m, 5H); MS: (M⁺+Na) 352;

cis-4-(2-benzoylamino-2S-cyanomethylcarbamoyl-ethyl)cyclohexyl acetate
(Compound 243); MS: (M⁺+Na) 394, (M⁺-CH₃COO) 312;

15 N-[(cyanomethylcarbamoyl)(phenethylsulfanyl)methyl]benzamide (Compound 244);
¹H NMR (DMSO): 9.14 (d, J = 10Hz, 1H), 9.01 (t, J = 7Hz, 1H), 7.94 (d, J = 9Hz, 2H), 7.5
(m, 3H), 7.2 (m, 5H), 5.88 (d, J = 10Hz, 1H), 4.22 (m, 2H), 2.90 (m, 4H); MS: m/e =
354.01;

N-[1S-cyanomethylcarbamoyl-2-(1-thiazol-2-ylpiperidin-4-yl)ethyl]benzamide
20 (Compound 245); ¹H NMR: (CDCl₃+10% CD₃OD) 7.77 (d, J=7Hz, 2H), 7.51-7.37 (m,
3H), 7.06 (d, J=3.6Hz, 1H), 6.48 (d, J=3.6Hz, 1H), 4.68 (t, J=7.3Hz, 1H), 4.14 (d,
J=17.3Hz, 1H), 4.01 (d, J=17.3Hz, 1H), 3.91-3.85 (m, 2H), 2.99-2.89 (m, 2H), 1.90-1.27
(m, 7H); MS: (M⁺+Na) 420;

N-[(cyanomethylcarbamoyl)(cyclohexylsulfanyl)methyl]benzamide (Compound 246);
25 ¹H NMR (DMSO): 9.10 (d, J = 10Hz, 1H), 8.94 (t, J = 6Hz, 1H), 7.92 (d, J = 9Hz, 2H),
7.50 (m, 3H), 5.80 (d, J = 10Hz, 1H), 4.19 (d, J = 6Hz, 2H), 2.96 (m, 1H), 2.00 (m, 1H),
1.88 (m, 1H), 1.67 (m 2H), 1.53 (m, 1H), 1.27 (m 5H); MS: m/e = 331.98;

N-cyanomethyl-3-cyclohexyl-2R-(2-ethoxyacetyl-amino)propionamide
(Compound 247);

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-3-methoxypropionamide

(Compound 248); ¹H NMR (CDCl₃): 7.68 (t, J=5.4Hz, 1H), 6.66 (d, J=7.9Hz, 1H), 4.52 (dd, J=9.4, 13.4Hz, 1H), 4.18 (dd, J=5.9, 17.6Hz, 1H), 4.06 (dd, J=5.9, 17.6Hz, 1H), 3.65 (m, 2H), 3.38 (s, 3H), 2.50 (t, J=5.7Hz, 2H), 0.8-1.70 (m, 13H);

5 cis-N-[1S-cyanomethylcarbamoyl-2-(4-methoxycyclohexyl)ethyl]benzamide

(Compound 249); ¹H NMR: (CDCl₃) 8.01 (s, 1H), 7.80 (d, J=7Hz, 2H), 7.55-7.42 (m, 3H), 6.84 (d, J=8.3Hz, 1H), 5.26 (m, 1H), 4.59 (d, J=17.2Hz, 1H), 4.14 (d, J=17.2Hz, 1H), 3.54 (m, 1H), 3.29 (s, 3H), 2.18-0.94 (m, 11H); MS: (M⁺+Na) 366;

N-(2-benzylsulfanyl-

10 1R-cyanomethylcarbamoyl-3-[3-(1-benzylpyrrolidin-3R-yl)-3-methylureido]benzamide

(Compound 250); ESI-MS m/z 585.3 (M+H⁺);

N-(2-benzylsulfanyl-

1R-cyanomethylcarbamoyl-3-[3-(1-benzylpyrrolidin-3S-yl)-3-methylureido]benzamide

(Compound 251); ESI-MS m/z 585.4 (M+H⁺);

15 N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl-ethyl)-

3-[3-(4-benzylpiperazin-1-ylcarbonyl)amino]benzamide (Compound 252); ESI-MS m/z 571.2 (M+H⁺);

N-(1R-cyanomethylcarbamoyl-2-pentafluorobenzylsulfanylethyl)benzamide

(Compound 253);

20 N-[1R-cyanomethylcarbamoyl-2-naphth-2-ylmethylsulfanylethyl]benzamide

(Compound 254); ¹H NMR (CDCl₃): 7.80 (m, 4H), 7.12-7.74 (m, 9H), 4.80 (m, 1H), 4.10 (m, 3H), 3.75 (s, 2H), 3.02 (m, 1H), 2.87 (m, 1H), 2.2-2.6 (m);

N-(2-benzylsulfanyl-1R-cyanomethylcarbamoyl-ethyl)-

3-(3-[1,3,4]thiadiazol-2-ylureido)benzamide (Compound 255); ¹H NMR (270 MHz,

25 DMSO-d₆) δ 2.78 (m, 1), 2.89 (m, 1), 3.79 (s, 2), 4.18 (d, 2), 4.71 (m, 1), 7.23-7.37 (m, 5), 7.45 (t, 1), 7.61 (d, 1), 7.71 (d, 1), 7.99 (s, 1), 8.75 (d, 1), 8.77 (t, 1), 9.08 (s, 1), 9.22 (s, 1); ESI-MS m/z 496.1 (M+H⁺);

N-[2-(4-chlorobenzylsulfanyl)-1R-cyanomethylcarbamoyl-ethyl]benzamide

(Compound 256); ¹H NMR: (DMSO) 8.85 (t, J=5Hz, 1H), 8.73 (d, J=8.4Hz, 1H), 7.92 (d,

J=7Hz, 2H), 7.60-7.47 (m, 3H), 7.40-7.33 (m, 4H), 4.69 (dd, J=5.2Hz, J=9.4Hz, 1H), 4.16 (s, 2H), 3.78 (s, 2H), 2.90 (dd, J=5.2Hz, J=13.6Hz, 1H), 2.77 (dd, J=9.6Hz, J=13.8Hz, 1H); MS: (M⁺+1) 388/390;

N-[1R-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]benzamide

- 5 (Compound 257); ¹H NMR: (DMSO) 8.87 (t, J=5.4Hz, 1H), 8.74 (d, J=8.2Hz, 1H), 7.92 (d, J=7Hz, 2H), 7.60-7.47 (m, 3H), 7.25-7.08 (m, 4H), 4.75 (m, 1H), 4.17 (d, J=5.7Hz, 2H), 3.80 (s, 2H), 2.98 (dd, J=5.2Hz, J=13.6Hz, 1H), 2.82 (dd, J=9.6Hz, J=13.8Hz, 1H), 2.31 (s, 3H); MS: (M⁺+1) 368;

N-[1R-cyanomethylcarbamoyl-2-(3,5-dimethylbenzylsulfanyl)ethyl]benzamide

- 10 (Compound 258); ¹H NMR: (DMSO) 8.86 (t, J=5.4Hz, 1H), 8.73 (d, J=8.2Hz, 1H), 7.93 (d, J=7Hz, 2H), 7.60-7.46 (m, 3H), 6.91 (s, 2H), 6.85 (s, 1H), 4.71 (m, 1H), 4.17 (d, J=5.7Hz, 2H), 3.70 (s, 2H), 2.92 (dd, J=5.4Hz, J=13.6Hz, 1H), 2.76 (dd, J=9.6Hz, J=13.8Hz, 1H), 2.22 (s, 6H); MS: (M⁺+1) 382;

N-[1R-cyanomethylcarbamoyl-2-(4-trifluoromethylbenzylsulfanyl)ethyl]benzamide

- 15 (Compound 259); ¹H NMR: (DMSO) 8.86 (t, J=5.4Hz, 1H), 8.74 (d, J=7.9Hz, 1H), 7.93 (d, J=7Hz, 2H), 7.68 (d, J=8.2Hz, 2H), 7.60-7.46 (m, 5H), 4.71 (m, 1H), 4.17 (m, 2H), 3.88 (s, 2H), 2.92 (dd, J=5.4Hz, J=13.4Hz, 1H), 2.79 (dd, J=9.6Hz, J=13.8Hz, 1H); MS: (M⁺+1) 422;

N-[1R-cyanomethylcarbamoyl-2-(4-trifluoromethoxybenzylsulfanyl)ethyl]benzamide

- 20 (Compound 260); ¹H NMR: (DMSO) 8.86 (t, J=5.4Hz, 1H), 8.74 (d, J=8.2Hz, 1H), 7.93 (d, J=7Hz, 2H), 7.60-7.42 (m, 5H), 7.31 (d, J=7.9Hz, 2H), 4.71 (m, 1H), 4.17 (d, J=5.7Hz, 2H), 3.83 (s, 2H), 2.92 (dd, J=5.4Hz, J=13.8Hz, 1H), 2.79 (dd, J=9.6Hz, J=13.8Hz, 1H); MS: (M⁺+1) 438;

N-[1R-cyanomethylcarbamoyl-

- 25 2-(4-trifluoromethylsulfanylbenzylsulfanyl)ethyl]benzamide (Compound 261); ¹H NMR: (DMSO) 8.86 (t, J=5.4Hz, 1H), 8.75 (d, J=8.2Hz, 1H), 7.92 (d, J=7Hz, 2H), 7.66 (d, J=7.9Hz, 2H), 7.60-7.45 (m, 5H), 4.72 (m, 1H), 4.17 (d, J=5.7Hz, 2H), 3.86 (s, 2H), 2.92 (dd, J=5.4Hz, J=13.8Hz, 1H), 2.80 (dd, J=9.6Hz, J=13.8Hz, 1H); MS: (M⁺+1) 454;

N-[1R-cyanomethylcarbamoyl-2-(3-nitrobenzylsulfanyl)ethyl]benzamide

(Compound 262); ¹H NMR: (DMSO) 8.83 (t, J=5Hz, 1H), 8.73 (d, J=7.7Hz, 1H), 8.21 (s, 1H), 8.09 (d, J=8Hz, 1H), 7.99 (m, 2H), 7.79 (d, J=7.7Hz, 1H), 7.63-7.45 (m, 4H), 4.66 (m, 1H), 4.14 (d, J=5Hz, 2H), 3.94 (s, 2H), 2.90-2.49 (m, 2H); MS: (M⁺+1) 399.2;

N-[1R-cyanomethylcarbamoyl-2-(3-nitrobenzylsulfanyl)ethyl]benzamide

5 (Compound 263); ¹H NMR (DMSO): 8.79 (m, 1H), 8.48 (d, J=5Hz, 1H), 7.93 (d, J=7Hz, 2H), 7.75 (dt, J=2,8Hz, 1H), 7.52 (m, 5H), 7.26 (m, 1H), 4.71 (m, 1H), 4.15 (m, 2H), 3.88 (s, 2H), 2.89 (m, 2H); MS: m/e=354.97;

N-(1R-cyanomethylcarbamoyl-2-pyrid-3-ylmethylsulfanylethyl)benzamide

(Compound 264); ¹H NMR (DMSO): 8.86 (t, J=6Hz, 1H), 8.74 (d, J=9Hz, 1H), 8.53 (d, J=2Hz, 1H), 8.44 (dd, J=5, 2Hz, 1H), 7.91 (m, 2H), 7.74 (m, 1H), 7.54 (m, 3H), 7.34 (m, 1H), 4.72 (m, 1H), 4.17 (m, 2H), 3.82 (s, 2H), 2.84 (m, 2H); MS: m/e=355.04;

N-(1R-cyanomethylcarbamoyl-2-pyrid-4-ylmethylsulfanylethyl)benzamide

(Compound 265); ¹H NMR (DMSO): 8.85 (t, J=6Hz, 1H), 8.75 (d, J=9Hz, 1H), 8.5 (m, 2H), 7.93 (m, 2H), 7.54 (m, 3H), 7.35 (m, 2H), 4.69 (m, 1H), 4.16 (d, J=6Hz, 2H), 3.8 (s, 15 = 2H), 2.91 (dd, J=6,15Hz, 1H), 2.79 (dd, J=10,15Hz, 1H); MS: m/e=355.02;

3-amino-N-(1S-cyanomethylcarbamoyl)-2-cyclohexylethylbenzamide

(Compound 266);

3-amino-N-(2-benzylsulfanyl-1R-cyanomethylcarbamoylethyl)benzamide

(Compound 267);

20 3-amino-N-(1S-cyanomethylcarbamoylpentyl)benzamide (Compound 268);

methyl 2S-benzoylamino-3-cyclohexylpropionylaminocynoacetate (Compound 269);

MS: (M⁺+Na) 394;

2S-benzoylamino-3-cyclohexylpropionylaminocynoacetic acid (Compound 270);

MS: (M⁺+1) 358;

25 N-[1R-cyanomethylcarbamoyl-2-(3,4-dichlorobenzylsulfanyl)ethyl]benzamide

(Compound 271); ¹H NMR (DMSO): 8.8 (d,t, 2H), 7.9 (d, J=8Hz, 2H), 7.8 (m, 3H), 7.1 (m, 4H), 4.7 (m, 1H), 4.2 (s, 2H), 3.7 (s, 2H), 2.9 (m, 1H), 2.7 (m, 1H), 2.3 (s, 3H);

MS: m/e=368.0;

N-[1R-cyanomethylcarbamoyl-2-(3-methylbenzylsulfanyl)ethyl]benzamide

(Compound 272);

N-[1R-cyanomethylcarbamoyl-2-(4-nitrobenzylsulfanyl)ethyl]benzamide

(Compound 273); ¹H NMR: (DMSO) 8.83 (t, J=5.1Hz, 1H), 8.72 (d, J=7.7Hz, 1H), 8.17 (d, J=8Hz, 2H), 7.89 (d, J=7Hz, 2H), 7.62-7.45 (m, 5H), 4.67 (m, 1H), 4.15 (d, J=5.4Hz, 2H), 3.92 (s, 2H), 2.89 (dd, J=5.4Hz, J=13.8Hz, 1H), 2.77 (dd, J=9.6Hz, J=13.8Hz, 1H); MS: (M⁺+1) 399.2;

N-[1R-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfanyl)ethyl]benzamide

(Compound 274); ¹H NMR (CDCl₃): 8.81 (m, 1H), 8.79 (d, J=8.0Hz, 1H), 7.95 (d, J=3.9Hz, 1H), 7.84 (m, 2H), 7.42-7.65 (m, 6H), 4.63 (m, 1H), 4.05 (m, 4H), 3.80 (m, 2H); MS: m/e (+1) 399.2;

N-[1R-cyanomethylcarbamoyl-2-(3-trifluoromethylbenzylsulfanyl)ethyl]benzamide

(Compound 275); ¹H NMR (DMSO): 8.86 (m, 1H), 8.74 (d, J=4.9Hz, 1H), 7.90 (d, J=8.4Hz, 2H), 4.72 (m, 1H), 4.15 (d, J=5.1Hz, 2H), 3.88 (s, 2H), 2.78 (m, 2H), 2.22-2.74 (m, 7H); MS: m/e (+1) 422.2;

N-[1R-cyanomethylcarbamoyl-2-(3-trifluoromethylbenzylsulfanyl)ethyl]benzamide

(Compound 276); ¹H NMR (DMSO): 8.81 (m, 1H), 8.76 (d, J=4.8Hz, 1H), 7.85 (d, J=8.4Hz, 2H), 7.10-7.55 (m, 7H), 4.7 (m, 1H), 4.15 (s, 2H), 3.80 (s, 2H), 2.80 (m, 2H); MS: m/e (+1) 438.2;

N-[1R-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]morpholine-4-carboxamide

(Compound 277); ¹H NMR (DMSO): 8.7 (t, J=6Hz, 1H), 7.2 (m, 4H), 6.67 (d, J=7.8Hz, 1H), 4.4 (m, 1H), 4.2 (s, 2H), 3.7 (s, 2H), 3.5 (t, 4H), 3.3 (t, 4H), 2.7 (m, 2H), 2.3 (s, 3H); MS m/e 377.2;

N-[1R-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfanyl)ethyl]morpholine-4-carboxamide

(Compound 278); ¹H NMR (DMSO): 8.67 (t, J=6Hz, 1H), 7.97 (d, J=8.1Hz, 1H), 7.5 (m, 4H), 4.28 (q, 1H), 4.1 (d, J=4Hz, 2H), 4.05 (m, 2H), 3.5 (t, 4H), 3.2 (t, 4H), 2.6 (m, 2H); MS m/e 408.4;

N-[1R-cyanomethylcarbamoyl-2-(3-nitrobenzylsulfanyl)ethyl]morpholine-4-carboxamide

(Compound 279); ¹H NMR (DMSO): 8.7 (t, J=3Hz, 1H), 8.2 (m, 2H), 7.7 (m, 2H), 6.77 (d, J=3Hz, 1H), 4.33 (m, 1H), 4.16 (m, 2H), 3.85 (d, J=2.4Hz, 2H), 3.4 (m,

8H), 2.6 (m, 2H); MS m/e 408;

N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)-1,1-dioxo-1 λ ⁶-thiomorpholine-4-carboxamide (Compound 280); ¹H NMR (DMSO): 8.5 (t, J=3Hz, 1H), 6.9 (d, J=3Hz, 1H), 4.11 (m, 3H), 3.8 (t, 4H), 3.1 (t, 4H), 1.8-0.8 (m, 13H); MS m/e 370.8;

- 5 N-(2-allylsulfanyl-1S-cyanomethylcarbamoylethyl)benzamide (Compound 281); ¹H NMR (DMSO): 8.72 (t, 1H), 8.65 (d, J=3Hz, 1H), 7.9 (d, 2H), 7.5 (m, 3H), 5.7 (m, 1H), 5.1 (m, 2H), 4.1 (d, J=3Hz, 2H), 2.8 (m, 2H); MS m/e 304.2;

- N-(1R-cyanomethylcarbamoyl)-2-(2-fluorobenzylsulfanyl)ethylbenzamide (Compound 282); ¹H NMR (DMSO): 8.85 (m, 1H), 8.72 (d, J=4.9Hz, 1H), 7.90 (d, J=8.3Hz, 2H), 7.10-7.63 (m, 7H), 4.62 (m, 1H), 4.08 (d, J=5.0Hz, 2H), 3.89 (s, 2H), 2.88 (m, 2H); MS: m/e (+1) 369.8;

- N-[2-(2-chlorobenzylsulfanyl)-1R-cyanomethylcarbamoylethyl]benzamide (Compound 283); ¹H NMR (DMSO): 8.80 (m, 1H), 8.75 (d, J=4.8, 1H), 7.95 (d, J=8.2Hz, 2H), 7.12-7.58 (m, 7H), 4.75 (m, 1H), 4.18 (d, J=4.8Hz, 2H), 3.85 (s, 2H), 2.8 (m, 2H); MS: m/e (+1) 388.2;

- N-[2-(2-bromobenzylsulfanyl)-1R-cyanomethylcarbamoylethyl]benzamide (Compound 284); ¹H NMR (DMSO): 8.85 (m, 1H), 8.73 (d, J=4.8Hz, 1H), 7.95 (d, J=8.2Hz, 2H), 7.4-7.65 (m, 5H), 7.37 (t, J=7.2Hz, 1H), 7.20 (t, J=7.2Hz, 1H), 4.70 (m, 1H), 4.08 (d, J=5.1Hz, 2H), 3.90 (s, 2H), 2.90 (m, 2H); MS: m/e (+1) 434.0;

- 20 N-[1R-cyanomethylcarbamoyl-2-(2-iodobenzylsulfanyl)ethyl]benzamide (Compound 285); ¹H NMR (DMSO): 8.86 (m, 1H), 8.74 (d, J=8.1Hz, 1H), 7.9 (d, J=8.4Hz, 2H), 7.83 (d, J=7.6Hz, 5H), 7.40-7.60 (m, 4H), 7.33 (t, J=7.7Hz, 1H), 6.99 (t, J=7.4Hz, 1H), 4.71 (m, 1H), 4.16 (d, J=5.5Hz, 2H), 3.83 (s, 2H), 2.88 (m, 2H); MS: m/e (+1) 480.0;

- N-[2-(4-tert-butyl-benzylsulfanyl)-1R-cyanomethylcarbamoylethyl]benzamide (Compound 286); ¹H NMR (CDCl₃): 8.16 (m, 1H), 7.79 (d, J=7.2Hz, 2H), 7.51 (t, J=7.3Hz, 2H), 7.40 (t, J=8.0Hz, 2H), 7.19-7.29 (m, 4H), 4.98 (m, 1H), 4.08 (m, 2H), 3.72 (m, 2H), 2.94 (m, 2H);

N-[3-(2-chlorophenylsulfanyl)-1R-cyanomethylcarbamoylpropyl]benzamide (Compound 287); ¹H NMR (DMSO): 8.73 (m, 2H), 7.92 (m, 2H), 7.38-7.56 (m, 5H), 7.32

(t,J=5.9Hz, 1H), 7.18 (t,J=5.9Hz, 1H), 4.64 (m, 1H), 4.14 (d, J=5.8Hz, 2H), 3.07 (m, 2H), 2.12 (m, 2H); MS:m/e (+1) = 385.9;

N-(1R-cyanomethylcarbamoyl-3-o-tolylsulfanylpropyl)benzamide (Compound 288);

¹H NMR (DMSO): 8.70 (m, 2H), 7.92 (m, 2H), 7.45-7.60 (m, 3H), 7.30 (d,J=13.3Hz, 1H), 7.05-7.21 (m, 3H), 4.61 (dd, J=7.7Hz, 1H), 4.13 (d, J=5.4Hz, 2H), 3 (m, 2H), 2.28 (s, 3H), 2.10 (m, 2H); MS:m/e (+1) = 366.0;

N-(1R-cyanomethylcarbamoyl-3-pyrid-2-ylsulfanylpropyl)benzamide

(Compound 289); ¹H NMR (DMSO): 8.70 (m, 2H), 8.39 (m, 1H), 7.95 (d,J=13.5, 2H), 7.45-7.68 (m, 4H), 7.29 (d,J=13.5Hz, 1H), 7.10 (m, 1H), 4.59 (m, 1H), 4.13 (d,J=5.7Hz, 2H), 3.20 (m, 2H), 2.14 (m, 2H); MS:m/e (+1) = 353.0;

tert-butyl 4-(1R-cyanomethylcarbamoyl-

2-pyrid-2-ylmethylethylsulfanylcyclohexylcarbamoyl)piperidine-1-carboxylate (Compound 290); ¹H NMR (DMSO): 8.72 (t,J=6.5Hz, 1H), 8.48 (d,J=5.2Hz, 1H), 8.21 (d,J=11.8Hz, 1H), 7.75 (t,J=6.5Hz, 1H), 7.38 (d,J=7.9Hz, 1H), 7.25 (m, 1H), 4.80 (m, 1H), 4.14 (d,J=6.6Hz, 2H), 3.93 (d,J=13.6Hz, 2H), 3.85 (s, 2H), 3.33 (s, 4H), 2.56-2.83 (m, 4H), 2.35 (m, 1H), 1.35 (s, 9H); MS:m/e (+1) = 461.4;

N-(1R-cyanomethylcarbamoyl-3-pyrid-4-ylsulfanylpropyl)benzamide

(Compound 291); ¹H NMR (DMSO): 8.73 (m, 2H), 8.35 (d,J=6.2Hz, 2H), 7.95 (m, 2H), 7.51 (m, 3H), 7.28 (d,J=6.2Hz, 2H), 4.62 (q,J=7.9Hz, 1H), 4.14 (d,J=5.7Hz, 2H), 3.13 (m, 2H), 2.14 (m, 2H); MS:m/e (+1) = 355.0;

N-[1-(Cyanomethyl-carbamoyl)-2-cycloheptyl-ethyl]-benzamide (Compound 292);

and

2-Benzylamino-N-cyanomethyl-3-cyclohexyl-propionamide (Compound 293).

EXAMPLE 11

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising:

5 *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was

10 added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity with a K_i of less than or equal to 10 μ M.

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EXAMPLE 12

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K

20 (0.0906 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress

25 curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed

to exhibit cathepsin K inhibitory activity with a K_i of less than or equal to 10 μM .

EXAMPLE 13

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of
5 dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL , comprising: MES,
50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in
25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10
seconds on a shaker plate, covered and incubated for 30 minutes at room temperature.
Z-Phe-Arg-AMC (1 nMoles in 25 μL of assay buffer) was added to the assay solutions and
10 hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent
inhibition constants (K_i) were calculated from the enzyme progress curves using standard
mathematical models.

Compounds of the invention were tested by the above-described assay and observed
to exhibit cathepsin L inhibitory activity with a K_i of less than or equal to 10 μM .

15

EXAMPLE 14

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of
dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL , comprising: MES,
50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles
20 in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10
seconds on a shaker plate, covered and incubated for 30 minutes at room temperature.
Z-Val-Val-Arg-AMC (9 nMoles in 25 μL of assay buffer) was added to the assay solutions
and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent
inhibition constants (K_i) were calculated from the enzyme progress curves using standard
25 mathematical models.

Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin S inhibitory activity with a K_i of less than or equal to 10 μ M.

EXAMPLE 15

Ovalbumin Challenge Mouse

- 5 C57 mice (female) were sensitised with ovalbumin (10 μ g, i.p.) administered together with aluminium hydroxide adjuvant (20 mg, i.p.) on days 0 and 12. Mice are challenged on either day 22, 23 or 24 by exposure for 60 minutes to an aerosol of ovalbumin (10 g / l) twice, 4 hours apart. Mice are dosed p.o. with either vehicle 5 ml/kg (0.5%MC/0.2 % Tween 80 in H₂O) or test compound at 0, 8, 23.5 29, 33, 48 and 56 hours.
- 10 Mice were euthanized with pentobarbitone i.p. after 86 hours (72 hours after the first challenge). The lungs were insufflated for histological examination as soon as possible after euthanization. Lungs were insufflated with 10% neutral buffered formalin (NBF), at 30 cm water pressure. The lungs were removed and placed in pots of 10% NBF. After fixation in 10% NBF for a minimum of 24 hours the lungs were processed through graded alcohols to wax.
- 15 The lungs were blocked longitudinally and one 2 μ m section for each animal was cut at the level of the main bronchi. Sections then were stained with haematoxylin and eosin. Pathological assessment of sections is performed and a grading is assigned.

Histopathological evaluation of the lung tissue demonstrate a dose dependant anti-inflammatory effect on vascular and mucosal beds after treatment with compounds of the invention between 0.03 and 30 mg/kg.

20

EXAMPLE 16

Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

	Compound of Formula I	10-100 mg
5	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
	Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

10	Compound of Formula I	0.1-10 mg
	Dextrose Monohydrate	q.s. to make isotonic
	Citric Acid Monohydrate	1.05 mg
	Sodium Hydroxide	0.18 mg
	Water for Injection	q.s. to 1.0 mL

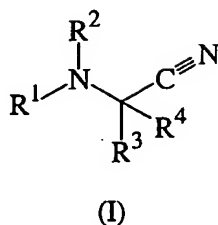
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TABLET FORMULATION

	Compound of Formula I	1%
	Microcrystalline Cellulose	73%
	Stearic Acid	25%
20	Colloidal Silica	1%.

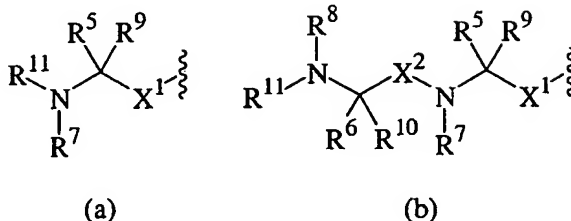
WE CLAIM:

1. A compound of Formula (I):



in which:

- 5 R^1 is a group of Formula (a) or (b):



wherein:

X^1 and X^2 independently are $-C(O)-$ or $-CH_2S(O)_2-$;

R^5 and R^6 are hydrogen or (C_{1-6}) alkyl;

- 10 R^7 and R^8 are hydrogen or (C_{1-6}) alkyl or as defined below;

R^9 and R^{10} independently are (i) (C_{1-6}) alkyl optionally substituted with cyano, halo or nitro or (ii) a group selected from $-X^3NR^{12}R^{12}$, $-X^3NR^{12}C(O)OR^{12}$, $-X^3NR^{12}C(O)NR^{12}R^{12}$, $-X^3NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^3OR^{12}$, $-X^3SR^{12}$, $-X^3C(O)OR^{12}$, $-X^3C(O)NR^{12}R^{12}$, $-X^3S(O)_2NR^{12}R^{12}$, $-X^3P(O)(OR^{12})OR^{12}$, $-X^3OP(O)(OR^{12})OR^{12}$, $-X^3NR^{12}C(O)R^{13}$, $-X^3S(O)R^{13}$, $-X^3S(O)_2R^{13}$, $-X^3C(O)R^{13}$, $-X^3C(O)R^{14}$, $-X^3C(O)OR^{14}$, $-X^3OC(O)R^{14}$, $-X^3NR^{15}C(O)R^{14}$, $-X^3NR^{15}C(O)OR^{14}$, $-X^3C(O)NR^{14}R^{15}$, $-X^3S(O)_2NR^{14}R^{15}$, $-X^3NR^{15}C(O)NR^{14}R^{15}$, $-X^3NR^{15}C(NR^{15})NR^{14}R^{15}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4OR^{14}$, or $-X^4NR^{14}R^{15}$, wherein X^3 is (C_{1-6}) alkylene, X^4 is a bond or (C_{1-6}) alkylene, R^{12} at each

occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (iii) a group selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR⁴)OR¹², -X⁴OP(O)(OR¹²)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁹ taken together with R⁷ and/or R¹⁰ taken together with R⁸ form

trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene; and

R^{11} is $-X^5X^6R^{18}$, wherein X^5 is $-C(O)-$, $-C(O)C(O)-$ or $-S(O)_2-$, X^6 is a bond, $-O-$ or $-NR^{19}-$, wherein R^{19} is hydrogen or (C_{1-6}) alkyl, and R^{18} is

5 (i) (C_{1-10}) alkyl optionally substituted by cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-OR^{20}$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-NR^{20}R^{21}$,
10 $-NR^{21}C(O)R^{20}$, $-NR^{21}C(O)OR^{20}$, $-NR^{21}C(O)NR^{20}R^{21}$ or $-NR^{21}C(NR^{21})NR^{20}R^{21}$, wherein R^{12} and R^{13} are as defined above, R^{20} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-6}) alkyl and R^{21} at each occurrence independently is hydrogen or (C_{1-6}) alkyl, or

15 (ii) (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-6}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by

20 $-X^4OR^{22}$, $-X^4SR^{22}$, $-X^4S(O)R^{22}$, $-X^4S(O)_2R^{22}$, $-X^4C(O)R^{22}$, $-X^4C(O)OR^{22}$, $-X^4C(O)NR^{22}R^{23}$, $-X^4NR^{22}R^{23}$, $-X^4NR^{23}C(O)R^{22}$, $-X^4NR^{23}C(O)OR^{22}$, $-X^4NR^{23}C(O)NR^{22}R^{23}$ or $-X^4NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^4 is as defined above, R^{22} is (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence

25 independently is hydrogen or (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$,

$-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$,
 $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and
 R^{13} are as defined above;

R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;

5 R^3 is hydrogen, (C_{1-6}) alkyl or as defined below; and

R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl is optionally substituted with
cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$,
 $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$,
10 $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$,
 $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or
 $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} , R^{13} , R^{14} and R^{15} are as defined above, or (ii) a group
selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and
15 hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$,
 $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$,
 $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$,
20 wherein X^4 , R^{16} and R^{17} are as defined above; wherein within R^9 and/or R^{10} any alicyclic or
aromatic ring system present may be substituted further by 1 to 5 radicals independently
selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro,
 $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$,
 $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$,
25 $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$,
 $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and R^{13} are as defined above, or

R^4 and R^2 taken together form trimethylene, tetramethylene or
phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or

R^4 and R^3 together with the carbon atom to which both R^4 and R^3 are attached form

(C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 in which:

5 R¹ is a group of Formula (a) wherein within Formula (a):

X¹ is -C(O)-;

R⁵ is hydrogen or (C₁₋₆)alkyl;

R⁷ is hydrogen or methyl;

R⁹ is (i) (C₁₋₆)alkyl optionally substituted with -OR¹⁴, -SR¹⁴, -S(O)R¹⁴,
 10 -S(O)₂R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, -OC(O)R¹⁴, -NR¹⁴R¹⁵, -NR¹⁵C(O)R¹⁴,
 -NR¹⁵C(O)OR¹⁴, -C(O)NR¹⁴R¹⁵, -S(O)₂NR¹⁴R¹⁵, -NR¹⁵C(O)NR¹⁴R¹⁵ or
 -NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, wherein R¹⁴ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl,
 (C₉₋₁₀)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is
 15 hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X³OR¹⁶, -X³SR¹⁶, -X³S(O)R¹⁶, -X³S(O)₂R¹⁶,
 -X³C(O)R¹⁶, -X³C(O)OR¹⁶, -X³OC(O)R¹⁶, -X³NR¹⁶R¹⁷, -X³NR¹⁷C(O)R¹⁶,
 -X³NR¹⁷C(O)OR¹⁶, -X³C(O)NR¹⁶R¹⁷, -X³S(O)₂NR¹⁶R¹⁷, -X³NR¹⁷C(O)NR¹⁶R¹⁷ or
 20 -X³NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X³ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or
 (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)polycycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₀)polycycloaryl(C₀₋₆)alkyl, or (ii) a group selected from
 (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl,
 25 hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)polycycloaryl(C₀₋₆)alkyl and
 hetero(C₈₋₁₀)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X³OR¹⁶, -X³SR¹⁶, -X³S(O)R¹⁶, -X³S(O)₂R¹⁶,

$-X^3C(O)R^{16}$, $-X^3C(O)OR^{16}$, $-X^3OC(O)R^{16}$, $-X^3NR^{16}R^{17}$, $-X^3NR^{17}C(O)R^{16}$,
 $-X^3NR^{17}C(O)OR^{16}$, $-X^3C(O)NR^{16}R^{17}$, $-X^3S(O)_2NR^{16}R^{17}$, $-X^3NR^{17}C(O)NR^{16}R^{17}$ or
 $-X^3NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein X^3 , R^{16} and R^{17} are as defined above; wherein
 5 within R^9 any alicyclic or aromatic ring system present may be substituted further by 1
 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo,
 halo-substituted (C_{1-4}) alkyl, nitro, $-X^3NR^{12}R^{12}$, $-X^3NR^{12}C(O)OR^{12}$,
 $-X^3NR^{12}C(O)NR^{12}R^{12}$, $-X^3NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^3OR^{12}$, $-X^3SR^{12}$,
 $-X^3C(O)OR^{12}$, $-X^3C(O)NR^{12}R^{12}$, $-X^3S(O)_2NR^{12}R^{12}$, $-X^3P(O)(OR^3)OR^{12}$,
 $-X^3OP(O)(OR^3)OR^{12}$, $-X^3OC(O)R^{13}$, $-X^3NR^{12}C(O)R^{13}$, $-X^3S(O)R^{13}$, $-X^3S(O)_2R^{13}$
 10 and $-X^3C(O)R^{13}$, wherein X^3 is as defined above, R^{12} at each occurrence
 independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{13} is
 (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl; and
 R^{11} is $-X^4X^5R^{18}$, wherein X^4 is $-C(O)-$ or $-S(O)_2-$, X^5 is a bond, $-O-$ or
 $-NR^{19}-$, wherein R^{19} is hydrogen or (C_{1-6}) alkyl, and R^{18} is (i) (C_{1-10}) alkyl or
 15 (ii) (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl,
 wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by
 $-X^9OR^{24}$, $-X^9C(O)R^{24}$, $-X^9C(O)OR^{24}$, $-X^9C(O)NR^{24}R^{25}$, $-X^9NR^{24}R^{25}$,
 20 $-X^9NR^{25}C(O)R^{24}$, $-X^9NR^{25}C(O)OR^{24}$, $-X^9NR^{25}C(O)NR^{24}R^{25}$ or
 $-X^9NR^{25}C(NR^{25})NR^{24}R^{25}$, wherein X^9 is a bond or (C_{1-6}) alkylene, R^{24} is
 (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or
 hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{25} is hydrogen or (C_{1-6}) alkyl, wherein within R^{11} any
 alicyclic or aromatic ring system present may be substituted further by 1 to 5
 25 substituents independently selected from (C_{1-6}) alkyl, halo, halo-substituted (C_{1-4}) alkyl,
 $-OR^{12}$, $-X^3SR^{12}$, $-C(O)OR^{12}$ and $-X^3NR^{12}C(O)OR^{12}$, wherein X^3 is a bond or
 (C_{1-6}) alkylene and R^{14} is hydrogen or (C_{1-6}) alkyl;
 R^2 is hydrogen;
 R^3 is hydrogen or (C_{1-4}) alkyl or taken with R^4 together with the carbon atom to which

both R³ and R⁴ are attached forms (C₃₋₈)cycloalkylene; and

R⁴ is hydrogen or as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

5 3. The compound of Claim 2 in which:

R¹ is a group of Formula (a) wherein within Formula (a):

R⁵ and R⁷ both are hydrogen;

10 R⁹ is (i) (C₁₋₆)alkyl optionally substituted with -OR¹⁴ or -SR¹⁴, wherein R¹⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl, biphenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, or (ii) a group selected from (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl, biphenyl(C₀₋₆)alkyl or hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl; wherein within R⁹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X³NR¹²R¹², -X³NR¹²C(O)OR¹²,
15 -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR³)OR¹², -X³OP(O)(OR³)OR¹², -X³OC(O)R¹³, -X³OC(O)R¹³, -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³ and -X³C(O)R¹³, wherein X³ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl; and

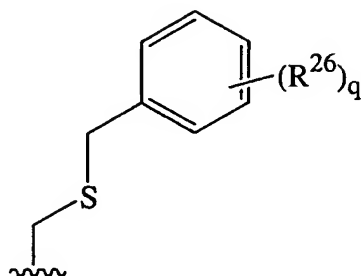
20 R¹¹ is -X⁴X⁵R¹⁸, wherein X⁴ is -C(O)-, X⁵ is a bond and R¹⁸ is (i) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl or (ii) phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said phenyl or heteroaryl is substituted by
25 -X⁹OR²⁴, -X⁹C(O)R²⁴, -X⁹C(O)OR²⁴, -X⁹C(O)NR²⁴R²⁵, -X⁹NR²⁴R²⁵, -X⁹NR²⁵C(O)R²⁴, -X⁹NR²⁵C(O)OR²⁴, -X⁹NR²⁵C(O)NR²⁴R²⁵ or -X⁹NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁹ is a bond or (C₁₋₆)alkylene, R²⁴ is phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ is hydrogen or (C₁₋₆)alkyl,

wherein within R^{11} any aromatic ring system present may be substituted further by 1 to 5 substituents independently selected from (C_{1-6}) alkyl, halo, halo-substituted (C_{1-4}) alkyl, $-OR^{12}$, $-X^3SR^{12}$, $-C(O)OR^{12}$ and $-X^3NR^{12}C(O)OR^{12}$ wherein X^3 is a bond or (C_{1-6}) alkylene and R^{12} is hydrogen or (C_{1-6}) alkyl; and

5 R^3 and R^4 are both hydrogen; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

10 4. The compound of Claim 3 in which within Formula (a) R^9 is cyclohexylmethyl, wherein said cyclohexyl may be substituted by 1 to 5 radicals independently selected from (C_{1-4}) alkyl, (C_{1-6}) alkylidene or $-X^3OC(O)R^{13}$, or phenylmethylsulfanylmethyl or phenylsulfanylethyl, wherein said phenyl may be substituted by 1 to 5 radicals independently selected from (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-OR^{12}$, $-SR^{12}$ and
15 $-C(O)OR^{12}$, wherein R^{12} is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl; and R^{11} is benzoyl, furylcarbonyl, phenyloxybenzoyl, pyridylthienylcarbonyl, benzoylbenzoyl, thienylcarbonyl, morpholinylcarbonyl, phenyluriedobenzoyl, cyclohexenylcarbonyl or piperazinylcarbonyl, wherein within R^{11} any aromatic ring system present may be substituted further by 1 to 2
20 substituents independently selected from (C_{1-6}) alkyl, *tert*-butoxycarbonylamino, *tert*-butoxycarbonylaminomethyl, bromo, chloro, ethoxy, fluoro, hydroxy, methoxy and methylsulfanyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

5. The compound of Claim 4 in which within Formula (a), R^9 is a group having the following formula:



in which q is 0 to 5 and R^{26} at each occurrence is independently selected from (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-OR^{12}$, $-SR^{12}$ and $-C(O)OR^{12}$, wherein R^{12} is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

6. The compound of Claim 3 in which within Formula (a), R^9 is

10 benzylsulfanylmethyl, 2-bromobenzylsulfanylmethyl, 2-chlorobenzylsulfanyl, 2-(2-chlorophenylsulfanyl)ethyl, cyclohexyl, 4-ethylidenecyclohexyl, 2-iodobenzylsulfanylmethyl, 2-methylbenzylsulfanylmethyl, 3-methyl-3-trifluorocarbonyloxycyclohexylmethyl, 4-methylenecyclohexylmethyl or 2-nitrobenzylsulfanylmethyl and R^{11} is 4-*tert*-butoxycarbonylaminobenzoyl,

15 3-*tert*-butoxycarbonylaminomethylbenzoyl, 2-(3,5-dimethoxyphenyl)thiazol-4-ylcarbonyl, fur-3-ylcarbonyl, 4-methoxybenzoyl, 3-methylbenzoyl, 3-phenoxybenzoyl, 5-pyrid-2-ylthien-2-ylcarbonyl, 3-benzoylbenzoyl, 4-methylbenzoyl, thien-2-ylcarbonyl, morpholin-4-ylcarbonyl, 5-bromothien-2-ylcarbonyl, 5-chlorothien-2-ylcarbonyl, 5-methylthien-2-ylcarbonyl, 2-(2-chloro-6-methylphenyl)ureidobenzoyl, cyclohexyl-1-en-1-ylcarbonyl, 3-ethoxybenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl and piperidin-1-ylcarbonyl;

20 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and

mixtures of isomers; and the pharmaceutically acceptable salts thereof.

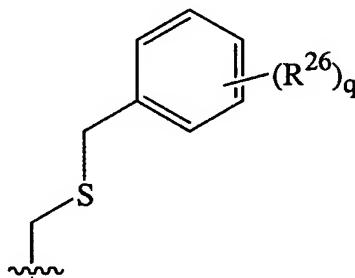
7. The compound of Claim 6 selected from a group consisting of:
N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)-4-hydroxybenzamide;
N-[2-(2-bromobenzylsulfanyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
5 *N*-[1*R*-cyanomethylcarbamoyl-2-(2-iodobenzylsulfanyl)ethyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(2-cyanobenzylsulfanyl)ethyl]morpholine-
4-carboxamide;
N-[3-(2-chlorophenylsulfanyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
N-[1*R*-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfanyl)ethyl]morpholine-
10 4-carboxamide
N-[1*R*-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]morpholine-
4-carboxamide; and
N-[1*R*-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]benzamide; and the
N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and
15 mixtures of isomers; and the pharmaceutically acceptable salts thereof.
8. A pharmaceutical composition comprising a compound of Claim 1, or a
N-oxide derivative, prodrug derivative, individual isomer, mixture of isomers, or a
pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.
9. A method of treating a disease in an animal in which cysteine protease activity
20 contributes to the pathology and/or symptomatology of the disease, which method comprises
administering to the animal a therapeutically effective amount of compound of Claim 1; or a
N-oxide derivative, prodrug derivative, individual isomer or mixture of isomers or a
pharmaceutically acceptable salt thereof.
10. The method of Claim 9 in which the cysteine protease is cathepsin S.

11. The method of Claim 10 in which the disease is an autoimmune disorder, allergic disorder, allogeneic immune response, a disorder involving excessive elastolysis, cardiovascular disorders or a disorder involving fibril formation.

12. The method of Claim 11 in which the disorder is selected from juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis, asthma, organ transplant or tissue graft rejections, chronic obstructive pulmonary disease, bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonitis, plaque rupture, atheroma and systemic amyloidosis.

13. A compound according to claim 1 in which R^1 is a group of formula (a) wherein X^1 is $-CH_2S(O)_2-$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

14. A compound according to any one of claims 1-3 and 13 in which R^1 is a group of formula (a) wherein R^9 is a group having the formula



in which q is 0 to 5 and R^{26} at each occurrence is independently selected from (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-OR^{12}$, $-SR^{12}$ and $-C(O)OR^{12}$, wherein R^{12} is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{13} is (C_{1-6}) alkyl or halo-substituted

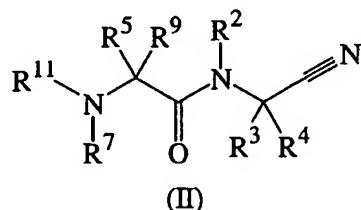
(C₁₋₃)alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

15. A compound according to claim 14 in which at least one R²⁶ group is attached at the benzene ring 2-position; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

16. A compound according to claim 15 in which the benzene ring is substituted by one R²⁶ group at the 2-position wherein R²⁶ is selected from at each occurrence is independently selected from (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -OR¹², -SR¹² and -C(O)OR¹², wherein R¹² is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

17. A compound according to claim 16 in which R²⁶ is difluoromethoxy; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

18. A compound of Formula (II):



wherein:

- 20 R² is hydrogen or (C₁₋₆)alkyl or as defined below;

R^3 is hydrogen, (C_{1-6}) alkyl or as defined below;

- R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl optionally is substituted with cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$, $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl, R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl, R^{14} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl and R^{15} is hydrogen or (C_{1-6}) alkyl, and wherein within R^{14} said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein X^4 is a bond or (C_{1-6}) alkylene, R^{16} is hydrogen or (C_{1-6}) alkyl and R^{17} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, or (ii) a group selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein X^4 , R^{16} and R^{17} are as defined above; wherein within R^4 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from

(C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹²,
 -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹²,
 -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR³)OR¹²,
 -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and
 5 -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁴ and R² taken together form trimethylene, tetramethylene or
 phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or
 R⁴ and R³ together with the carbon atom to which both R⁴ and R³ are attached form
 (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

10 R⁵ is hydrogen or (C₁₋₆)alkyl;

R⁷ is hydrogen or (C₁₋₆)alkyl;

R⁹ is (C₆₋₁₂)aryl(C₁₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₁₋₆)alkyl, -X⁴OR¹⁴, -X⁴SR¹⁴,
 -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴ or -X⁴NR¹⁴R¹⁵, wherein X⁴, R¹⁴ and R¹⁵ are as defined above and
 wherein within R⁹ said aryl or heteroaryl ring optionally is substituted by 1 to 5 radicals

15 independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro,
 -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹²,
 -X⁴OR¹², -X⁴SR¹², -X⁴C(O)R¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹²,
 -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³,
 -X⁴S(O)₂R¹³, wherein X⁴, R¹² and R¹³ are as defined above; and

20 R¹¹ is -X⁵X⁶R¹⁸, wherein X⁵ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁶ is a bond, -O-
 or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is (i) (C₁₋₁₀)alkyl optionally
 substituted by cyano, halo, nitro, -NR¹²R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹²,
 -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹²,
 -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³,
 25 -OR²⁰, -SR²⁰, -S(O)R²⁰, -S(O)₂R²⁰, -C(O)R²⁰, -C(O)OR²⁰, -C(O)NR²⁰R²¹, -NR²⁰R²¹,
 -NR²¹C(O)R²⁰, -NR²¹C(O)OR²⁰, -NR²¹C(O)NR²⁰R²¹ or -NR²¹C(NR²¹)NR²⁰R²¹, wherein
 R¹² and R¹³ are as defined above, R²⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²¹ at each occurrence

- independently is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or
- (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or
- 5 hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by -X⁴OR²², -X⁴SR²², -X⁴S(O)R²², -X⁴S(O)₂R²², -X⁴C(O)R²², -X⁴C(O)OR²², -X⁴C(O)NR²²R²³, -X⁴NR²²R²³, -X⁴NR²³C(O)R²², -X⁴NR²³C(O)OR²², -X⁴NR²³C(O)NR²²R²³ or -X⁴NR²³C(NR²³)NR²²R²³, wherein X⁴ is as defined above, R²² is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or
- 10 hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²³ at each occurrence independently is hydrogen or (C₁₋₆)alkyl; wherein within R¹¹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.
- 20 19. The compound of Claim 18 in which:
- R² is hydrogen;
- R³ is hydrogen, methyl or taken with R⁴ together with the carbon atom to which both R³ and R⁴ are attached forms (C₃₋₈)cycloalkylene;
- R⁴ is hydrogen, methyl or as defined above;
- 25 R⁵ is hydrogen or (C₁₋₆)alkyl;
- R⁷ is hydrogen or methyl;
- R⁹ represents (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴ or -X⁴NR¹⁴R¹⁵, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁴ is

(C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl and R¹⁵ is hydrogen or (C₁₋₆)alkyl, and wherein within R⁹ said aryl or heteroaryl ring optionally is substituted by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴OR¹², -X⁴C(O)R¹², -X⁴SR¹², wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹² at
 5 each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and

R¹¹ is -X⁴X⁵R¹⁸, wherein X⁴ is -C(O)- or -S(O)₂-, X⁵ is a bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is (i) (C₁₋₁₀)alkyl or
 10 (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by -X⁹OR²⁴, -X⁹C(O)R²⁴, -X⁹C(O)OR²⁴, -X⁹C(O)NR²⁴R²⁵, -X⁹NR²⁴R²⁵, -X⁹NR²⁵C(O)R²⁴, -X⁹NR²⁵C(O)OR²⁴, -X⁹NR²⁵C(O)NR²⁴R²⁵ or -X⁹NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁹ is a bond or (C₁₋₆)alkylene,
 15 R²⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ is hydrogen or (C₁₋₆)alkyl, wherein within R¹¹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 substituents independently selected from (C₁₋₆)alkyl, halo, halo-substituted (C₁₋₄)alkyl, -OR¹², -X³SR¹², -C(O)OR¹² and -X³NR¹²C(O)OR¹², wherein X³ is a bond or (C₁₋₆)alkylene and R¹⁴ is
 20 hydrogen or (C₁₋₆)alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

20. The compound of Claim 19 in which:

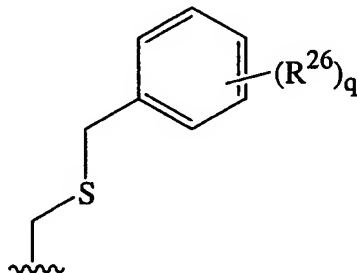
R³, R⁴, R⁵ and R⁷ each are hydrogen;

25 R⁹ represents benzyl, benzyloxymethyl, benzylsulfanylethyl, benzylsulfanylmethyl, benzylsulfinylmethyl, indolylmethyl, naphthylmethyl, phenethyl, phenoxyethyl, phenylamino, pyridylmethyl, pyridylsulfanylethyl, phenylsulfanylethyl, thiazolyl or thienyl, wherein within R⁹ the aromatic ring may be substituted further by 1 to 5 radicals independently selected from

- (C₁₋₆)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴OR¹², -X⁴C(O)R¹², -X⁴SR¹², wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and
- 5 R¹¹ is -X⁴X⁵R¹⁸, wherein X⁴ is -C(O)-, X⁵ is a bond and R¹⁸ is
- (i) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl or (ii) phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said phenyl or heteroaryl is substituted by -X⁹OR²⁴, -X⁹C(O)R²⁴, -X⁹C(O)OR²⁴, -X⁹C(O)NR²⁴R²⁵, -X⁹NR²⁴R²⁵, -X⁹NR²⁵C(O)R²⁴, -X⁹NR²⁵C(O)OR²⁴,
- 10 -X⁹NR²⁵C(O)NR²⁴R²⁵ or -X⁹NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁹ is a bond or (C₁₋₆)alkylene, R²⁴ is phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ is hydrogen or (C₁₋₆)alkyl, wherein within R¹¹ any aromatic ring system present may be substituted further by 1 to 5 substituents independently selected from (C₁₋₆)alkyl, halo, halo-substituted (C₁₋₄)alkyl, -OR¹², -X³SR¹², -C(O)OR¹² and -X³NR¹²C(O)OR¹² wherein X³ is a bond or (C₁₋₆)alkylene and R¹²
- 15 is hydrogen or (C₁₋₆)alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

21. The compound of Claim 20 in which R⁹ is a group having the following formula:

20



in which q is 0 to 5 and R²⁶ at each occurrence is independently selected from (C₁₋₄)alkyl,

cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -OR¹², -SR¹² and -C(O)OR¹², wherein R¹² is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

- 5 22. The compound of Claim 20 in which R⁹ is 4-aminobenzyl, benzyl, benzyloxymethyl, 2-benzylsulfanylethyl, benzylsulfanylmethyl, 2-bromobenzylsulfanylmethyl, 4-*tert*-butylbenzylsulfanylmethyl, 2-chlorobenzyl, 4-chlorobenzyl, 2-chlorobenzylsulfanylmethyl, 4-chlorobenzylsulfanylmethyl, 2-(2-chlorophenylsulfanyl)ethyl, 4-cyanobenzyl, 3,4-dichlorobenzylsulfanylmethyl, 1,6-dichlorobenzyl, 3,5-dimethylbenzylsulfanylmethyl, 2-fluorobenzyl, 4-fluorobenzyl, 10 2-fluorobenzylsulfanylmethyl, 1-formylindol-3-ylmethyl, indol-3-ylmethyl, 2-iodobenzylsulfanylmethyl, 2-methylbenzylsulfanylmethyl, 3-methylbenzylsulfanylmethyl, 3-methylbenzylsulfanylmethyl, 4-methylbenzylsulfanylmethyl, 2-(2-methylphenylsulfanyl)ethyl, 4-methoxybenzyl, 4-methoxybenzylsulfanylmethyl, 4-methoxybenzylsulfanylmethyl, naphth-2-ylmethyl, naphth-2-ylmethylsulfanylmethyl, 3-nitrobenzyl, 15 1-nitrobenzylsulfanylmethyl, 2-nitrobenzylsulfanylmethyl, 3-nitrobenzylsulfanylmethyl, 4-nitrobenzylsulfanylmethyl, 4-nitrobenzyl, pentafluorobenzylsulfanylmethyl, phenylamino, phenethyl, phenethyloxy, 2-phenoxyethyl, 2-phenoxyethyl 2-phenylsulfanylethyl, pyrid-4-ylmethyl, pyrid-2-ylmethylsulfanylmethyl, pyrid-3-ylmethylsulfanylmethyl, pyrid-4-ylmethylsulfanylmethyl, 2-pyrid-2-ylsulfanylethyl, 2-pyrid-4-ylsulfanylethyl, 20 thiazol-5-yl, thien-2-ylmethyl, 4-trifluoromethylbenzylsulfanylmethyl, 3-trifluoromethylbenzylsulfanylmethyl, 3-trifluoromethoxybenzylsulfanylmethyl, 4-trifluoromethoxybenzylsulfanylmethyl or 4-trifluorosulfanylbenzylsulfanylmethyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and 25 mixtures of isomers; and the pharmaceutically acceptable salts thereof.

23. The compound of Claim 22 which is selected a group from consisting of:
N-(2-benzylsulfanyl-1*R*-cyanomethylcarbamoylethyl)-4-hydroxybenzamide;

- N*-[2-(2-bromobenzylsulfanyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
N-[1*R*-cyanomethylcarbamoylethyl-2-(2-iodobenzylsulfanyl)]benzamide;
N-[1*R*-cyanomethylcarbamoylethyl-2-(2-cyanobenzylsulfanyl)]morpholine-4-carboxamide;
- 5 *N*-[3-(2-chlorophenylsulfanyl)-1*R*-cyanomethylcarbamoylethyl]benzamide;
N-[1*R*-cyanomethylcarbamoylethyl-2-(2-nitrobenzylsulfanyl)]morpholine-4-carboxamide
- N*-[1*R*-cyanomethylcarbamoylethyl-2-(2-methylbenzylsulfanyl)]morpholine-4-carboxamide; and
- 10 *N*-[1*R*-cyanomethylcarbamoylethyl-2-(2-methylbenzylsulfanyl)]benzamide; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.
24. A compound according to any preceding claim for use in therapy.
25. A compound or pharmaceutical composition according to any preceding
- 15 claim for use in treating a disease in an animal in which cysteine protease activity contributes to the pathology and/or symptomatology of the disease.
26. A compound or pharmaceutical composition for use according to claim 25 in which the cysteine protease is cathepsin S.
27. A compound or pharmaceutical composition for use according to claim 26 to
- 20 treat asthma.
28. Use of a compound according to any preceding claim for the manufacture of a medicament for the treatment of a disease in an animal in which cysteine protease activity contributes to the pathology and/or symptomatology of the disease.

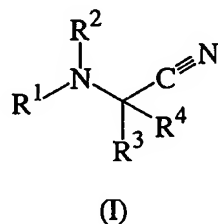
29. Use according to claim 28 for the treatment of a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease.

30. Use according to claim 29 for the treatment of asthma.

31. A compound or pharmaceutical composition according to any preceding claim and an anti-inflammatory agent as a combined preparation for simultaneous, separate or sequential use in the treatment of asthma.

32. A compound, pharmaceutical composition or use thereof substantially as herein described with reference to the Examples.

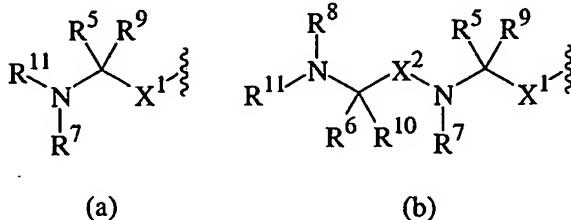
33. A method of treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease, which method comprising administering to the animal a therapeutically effective amount of a compound of Formula (I):



in which:

R¹ is a group of Formula (a) or (b):

15



wherein:

X¹ and X² independently are -C(O)- or -CH₂S(O)₂-;

R⁵ and R⁶ are hydrogen or (C₁₋₆)alkyl;

R⁷ and R⁸ are hydrogen or (C₁₋₆)alkyl or as defined below;

R⁹ and R¹⁰ independently are (i) (C₁₋₆)alkyl optionally substituted with cyano, halo or nitro or (ii) a group selected from -X³NR¹²R¹², -X³NR¹²C(O)OR¹²,

- 5 -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹²,
 -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR¹²)OR¹²,
 -X³OP(O)(OR¹²)OR¹², -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³, -X³C(O)R¹³,
 -X³C(O)R¹⁴, -X³C(O)OR¹⁴, -X³OC(O)R¹⁴, -X³NR¹⁵C(O)R¹⁴, -X³NR¹⁵C(O)OR¹⁴,
 -X³C(O)NR¹⁴R¹⁵, -X³S(O)₂NR¹⁴R¹⁵, -X³NR¹⁵C(O)NR¹⁴R¹⁵,
 10 -X³NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴OR¹⁴, or
 -X⁴NR¹⁴R¹⁵, wherein X³ is (C₁₋₆)alkylene, X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each
 occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³
 is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 15 (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is
 hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶,
 -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶,
 20 -X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or
 -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or
 (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (iii) a group selected from
 25 (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl,
 hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶,

$-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$,
 $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or
 $-X^4NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein X^4 , R^{16} and R^{17} are as defined above; wherein
 within R^9 and/or R^{10} any alicyclic or aromatic ring system present may be substituted
 5 further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene,
 cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$,
 $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$,
 $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^4)OR^{12}$,
 $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$
 10 and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and R^{13} are as defined above, or

R^9 taken together with R^7 and/or R^{10} taken together with R^8 form
 trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with
 hydroxy, oxo or methylene; and

R^{11} is $-X^5X^6R^{18}$, wherein X^5 is $-C(O)-$, $-C(O)C(O)-$ or $-S(O)_2-$, X^6 is a
 15 bond, $-O-$ or $-NR^{19}-$, wherein R^{19} is hydrogen or (C_{1-6}) alkyl, and R^{18} is

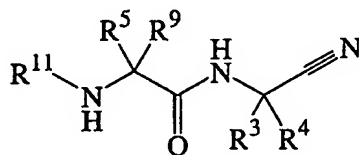
(i) (C_{1-10}) alkyl optionally substituted by cyano, halo, nitro, $-NR^{12}R^{12}$,
 $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$,
 $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-P(O)(OR^{12})OR^{12}$,
 $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-OR^{20}$, $-SR^{20}$,
 20 $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-NR^{20}R^{21}$,
 $-NR^{21}C(O)R^{20}$, $-NR^{21}C(O)OR^{20}$, $-NR^{21}C(O)NR^{20}R^{21}$ or $-NR^{21}C(NR^{21})NR^{20}R^{21}$,
 wherein R^{12} and R^{13} are as defined above, R^{20} is (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl,
 (C_{9-12}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-6}) alkyl and R^{21} at each
 25 occurrence independently is hydrogen or (C_{1-6}) alkyl, or

(ii) (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-6}) alkyl or
 hetero (C_{8-12}) bicycloaryl (C_{0-6}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl,

- wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by
 $-X^4OR^{22}$, $-X^4SR^{22}$, $-X^4S(O)R^{22}$, $-X^4S(O)_2R^{22}$, $-X^4C(O)R^{22}$, $-X^4C(O)OR^{22}$,
 $-X^4C(O)NR^{22}R^{23}$, $-X^4NR^{22}R^{23}$, $-X^4NR^{23}C(O)R^{22}$, $-X^4NR^{23}C(O)OR^{22}$,
 $-X^4NR^{23}C(O)NR^{22}R^{23}$ or $-X^4NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^4 is as defined
5 above, R^{22} is (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl,
phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence
independently is hydrogen or (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic
ring system present may be substituted further by 1 to 5 radicals independently
selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl,
10 nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$,
 $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$,
 $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, $-X^4OP(O)(OR^3)OR^{12}$, $-X^4OC(O)R^{13}$,
 $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and $-X^4C(O)R^{13}$, wherein X^4 , R^{12} and
 R^{13} are as defined above;
15 R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;
 R^3 is hydrogen, (C_{1-6}) alkyl or as defined below; and
 R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl is optionally substituted with
cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$,
20 $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$,
 $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$,
 $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or
 $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} , R^{13} , R^{14} and R^{15} are as defined above, or (ii) a group
selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
25 (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and
hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
selected from $-R^{16}$, $-X^4OR^{16}$, $-X^4SR^{16}$, $-X^4S(O)R^{16}$, $-X^4S(O)_2R^{16}$, $-X^4C(O)R^{16}$,
 $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$,

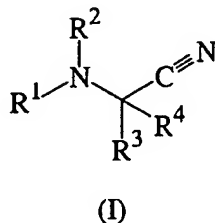
- X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷,
 wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or
 aromatic ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro,
 5 -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹²,
 -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹²,
 -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³,
 -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or
 R⁴ and R² taken together form trimethylene, tetramethylene or
 10 phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or
 R⁴ and R³ together with the carbon atom to which both R⁴ and R³ are attached form
 (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene; or an *N*-oxide derivative, prodrug
 derivative, individual isomer and mixtures of isomers; or a pharmaceutically acceptable salt
 thereof, but excluding compounds of the formula

15



- in which R³ and R⁴ are each hydrogen or (C₁₋₆)alkyl, or together with the carbon atom to
 which they are both attached form (C₃₋₅)cycloalkylene; R⁵ is hydrogen or (C₁₋₆)alkyl; R⁹ is
 (C₆₋₁₂)aryl(C₁₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₁₋₆)alkyl, (C₄₋₅)alkyl or cyclohexylmethyl; and R¹¹ is
 C(O)R¹⁸ wherein R¹⁸ is hetero(C₃₋₁₂)cycloalkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl.
 20

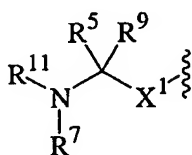
34. The use of a compound of Formula (I):



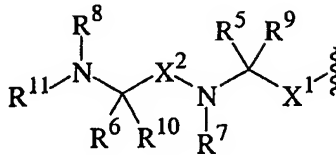
in which:

R¹ is a group of Formula (a) or (b):

5



(a)



(b)

wherein:

X¹ and X² independently are -C(O)- or -CH₂S(O)₂-;

R⁵ and R⁶ are hydrogen or (C₁₋₆)alkyl;

R⁷ and R⁸ are hydrogen or (C₁₋₆)alkyl or as defined below;

10 R⁹ and R¹⁰ independently are (i) (C₁₋₆)alkyl optionally substituted with cyano, halo or nitro or (ii) a group selected from -X³NR¹²R¹², -X³NR¹²C(O)OR¹², -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR¹²)OR¹², -X³OP(O)(OR¹²)OR¹², -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³, -X³C(O)R¹³, -X³C(O)R¹⁴, -X³C(O)OR¹⁴, -X³OC(O)R¹⁴, -X³NR¹⁵C(O)R¹⁴, -X³NR¹⁵C(O)OR¹⁴, -X³C(O)NR¹⁴R¹⁵, -X³S(O)₂NR¹⁴R¹⁵, -X³NR¹⁵C(O)NR¹⁴R¹⁵, -X³NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴OR¹⁴, or -X⁴NR¹⁴R¹⁵, wherein X³ is (C₁₋₆)alkylene, X⁴ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,

15

20

(C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶,
5 -X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶,
-X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or
-X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
(C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
10 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (iii) a group selected from
(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl,
hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and
hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
15 group selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶,
-X⁴C(O)R¹⁶, -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶,
-X⁴NR¹⁷C(O)OR¹⁶, -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or
-X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein
within R⁹ and/or R¹⁰ any alicyclic or aromatic ring system present may be substituted
20 further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene,
cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹²,
-X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹²,
-X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR⁴)OR¹²,
-X⁴OP(O)(OR¹²)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³
25 and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

R⁹ taken together with R⁷ and/or R¹⁰ taken together with R⁸ form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene; and

R¹¹ is -X⁵X⁶R¹⁸, wherein X⁵ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁶ is a

bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is

(i) (C₁₋₁₀)alkyl optionally substituted by cyano, halo, nitro, -NR¹²R¹²,
 -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹²,
 -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -P(O)(OR¹²)OR¹²,
 5 -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -OR²⁰, -SR²⁰,
 -S(O)R²⁰, -S(O)₂R²⁰, -C(O)R²⁰, -C(O)OR²⁰, -C(O)NR²⁰R²¹, -NR²⁰R²¹,
 -NR²¹C(O)R²⁰, -NR²¹C(O)OR²⁰, -NR²¹C(O)NR²⁰R²¹ or -NR²¹C(NR²¹)NR²⁰R²¹,
 wherein R¹² and R¹³ are as defined above, R²⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 10 (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²¹ at each
 occurrence independently is hydrogen or (C₁₋₆)alkyl, or

(ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl,
 15 hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl,
 wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by
 -X⁴OR²², -X⁴SR²², -X⁴S(O)R²², -X⁴S(O)₂R²², -X⁴C(O)R²², -X⁴C(O)OR²²,
 -X⁴C(O)NR²²R²³, -X⁴NR²²R²³, -X⁴NR²³C(O)R²², -X⁴NR²³C(O)OR²²,
 -X⁴NR²³C(O)NR²²R²³ or -X⁴NR²³C(NR²³)NR²²R²³, wherein X⁴ is as defined
 20 above, R²² is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl,
 phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²³ at each occurrence
 independently is hydrogen or (C₁₋₆)alkyl; wherein within R¹¹ any alicyclic or aromatic
 ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl,
 25 nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹²,
 -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹²,
 -X⁴S(O)₂NR¹²R¹², -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³,
 -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and
 R¹³ are as defined above;

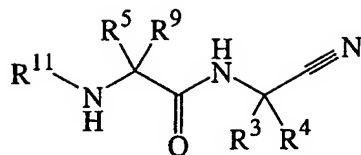
R² is hydrogen or (C₁₋₆)alkyl or as defined below;

R³ is hydrogen, (C₁₋₆)alkyl or as defined below; and

- R⁴ is (i) hydrogen or (C₁₋₆)alkyl, wherein said alkyl is optionally substituted with cyano, halo, nitro, -NR¹²R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹²,
 5 -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹²,
 -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³,
 -OR¹⁴, -SR¹⁴, -S(O)R¹⁴, -S(O)₂R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, -OC(O)R¹⁴, -NR¹⁴R¹⁵,
 -NR¹⁵C(O)R¹⁴, -NR¹⁵C(O)OR¹⁴, -C(O)NR¹⁴R¹⁵, -S(O)₂NR¹⁴R¹⁵, -NR¹⁵C(O)NR¹⁴R¹⁵ or
 -NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, wherein R¹², R¹³, R¹⁴ and R¹⁵ are as defined above, or (ii) a group
 10 selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
 selected from -R¹⁶, -X⁴OR¹⁶, -X⁴SR¹⁶, -X⁴S(O)R¹⁶, -X⁴S(O)₂R¹⁶, -X⁴C(O)R¹⁶,
 15 -X⁴C(O)OR¹⁶, -X⁴OC(O)R¹⁶, -X⁴NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)R¹⁶, -X⁴NR¹⁷C(O)OR¹⁶,
 -X⁴C(O)NR¹⁶R¹⁷, -X⁴S(O)₂NR¹⁶R¹⁷, -X⁴NR¹⁷C(O)NR¹⁶R¹⁷ or -X⁴NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷,
 wherein X⁴, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or
 aromatic ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro,
 20 -X⁴NR¹²R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹²,
 -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹²,
 -X⁴P(O)(OR³)OR¹², -X⁴OP(O)(OR³)OR¹², -X⁴OC(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³,
 -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein X⁴, R¹² and R¹³ are as defined above, or

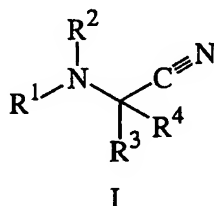
- R⁴ and R² taken together form trimethylene, tetramethylene or
 25 phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or

R⁴ and R³ together with the carbon atom to which both R⁴ and R³ are attached form
 (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene; or an *N*-oxide derivative, prodrug
 derivative, individual isomer and mixtures of isomers; or a pharmaceutically acceptable salt
 thereof, but excluding compounds of the formula



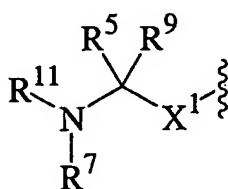
- in which R^3 and R^4 are each hydrogen or (C_{1-6}) alkyl, or together with the carbon atom to which they are both attached form (C_{3-5}) cycloalkylene; R^5 is hydrogen or (C_{1-6}) alkyl; R^9 is (C_{6-12}) aryl (C_{1-6}) alkyl, hetero (C_{5-12}) aryl (C_{1-6}) alkyl, (C_{4-5}) alkyl or cyclohexylmethyl; and R^{11} is
- 5 C(O) R^{18} wherein R^{18} is hetero (C_{3-12}) cycloalkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl, in the manufacture of a medicament for treating a disease in an animal in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease.

35. A process for preparing a compound of Formula I:

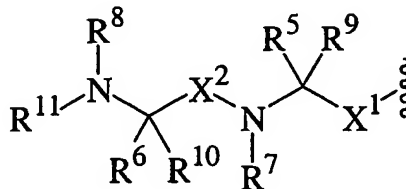


- 10 in which:

R^1 is a group of Formula (a) or (b):



(a)



(b)

wherein:

X^1 and X^2 independently are $-C(O)-$ or $-CH_2S(O)_2-$;

R⁵ and R⁶ are hydrogen or (C₁₋₆)alkyl;

R⁷ and R⁸ are hydrogen or (C₁₋₆)alkyl or as defined below;

R⁹ and R¹⁰ independently are (i) (C₁₋₆)alkyl optionally substituted with cyano, halo, nitro, -NR¹²R¹³, -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹²,

- 5 -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹²,
 -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³,
 -C(O)R¹³, -OR¹⁴, -SR¹⁴, -S(O)R¹⁴, -S(O)₂R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, -OC(O)R¹⁴,
 -NR¹⁴R¹⁵, -NR¹⁵C(O)R¹⁴, -NR¹⁵C(O)OR¹⁴, -C(O)NR¹⁴R¹⁵, -S(O)₂NR¹⁴R¹⁵,
 -NR¹⁵C(O)NR¹⁴R¹⁵ or -NR¹⁵C(NR¹⁵)NR¹⁴R¹⁵, wherein R¹² at each occurrence
 10 independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹³ is (C₁₋₆)alkyl
 or halo-substituted (C₁₋₃)alkyl, R¹⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁵ is
 hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁴ said cycloalkyl, heterocycloalkyl, aryl,
 15 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X³OR¹⁶, -X³SR¹⁶, -X³S(O)R¹⁶, -X³S(O)₂R¹⁶,
 -X³C(O)R¹⁶, -X³C(O)OR¹⁶, -X³OC(O)R¹⁶, -X³NR¹⁶R¹⁷, -X³NR¹⁷C(O)R¹⁶,
 -X³NR¹⁷C(O)OR¹⁶, -X³C(O)NR¹⁶R¹⁷, -X³S(O)₂NR¹⁶R¹⁷, -X³NR¹⁷C(O)NR¹⁶R¹⁷ or
 -X³NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X³ is a bond or (C₁₋₆)alkylene, R¹⁶ is hydrogen or
 20 (C₁₋₆)alkyl and R¹⁷ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (ii) a group selected from
 (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl,
 hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and
 25 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a
 group selected from -R¹⁶, -X³OR¹⁶, -X³SR¹⁶, -X³S(O)R¹⁶, -X³S(O)₂R¹⁶,
 -X³C(O)R¹⁶, -X³C(O)OR¹⁶, -X³OC(O)R¹⁶, -X³NR¹⁶R¹⁷, -X³NR¹⁷C(O)R¹⁶,
 -X³NR¹⁷C(O)OR¹⁶, -X³C(O)NR¹⁶R¹⁷, -X³S(O)₂NR¹⁶R¹⁷, -X³NR¹⁷C(O)NR¹⁶R¹⁷ or

-X³NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein X³, R¹⁶ and R¹⁷ are as defined above; wherein within R⁹ and/or R¹⁰ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X³NR¹²R¹², -X³NR¹²C(O)OR¹²,
 5 -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹²,
 -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹², -X³P(O)(OR³)OR¹²,
 -X³OP(O)(OR³)OR¹², -X³OC(O)R¹³, -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³
 and -X³C(O)R¹³, wherein X³, R¹² and R¹³ are as defined above, or

R⁹ taken together with R⁷ and/or R¹⁰ taken together with R⁸ form
 10 trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene; and

R¹¹ is -X⁴X⁵R¹⁸, wherein X⁴ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁵ is a bond, -O- or -NR¹⁹-, wherein R¹⁹ is hydrogen or (C₁₋₆)alkyl, and R¹⁸ is

(i) (C₁₋₁₀)alkyl optionally substituted by cyano, halo, nitro, -NR¹²R¹²,
 15 -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹²,
 -C(O)OR¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -P(O)(OR¹²)OR¹²,
 -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -OR²⁰, -SR²⁰,
 -S(O)R²⁰, -S(O)₂R²⁰, -C(O)R²⁰, -C(O)OR²⁰, -C(O)NR²⁰R²¹, -NR²⁰R²¹,
 -NR²¹C(O)R²⁰, -NR²¹C(O)OR²⁰, -NR²¹C(O)NR²⁰R²¹ or -NR²¹C(NR²¹)NR²⁰R²¹,

20 wherein R¹² and R¹³ are as defined above, R²⁰ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²¹ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or

(ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 25 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by -X³OR²², -X³SR²², -X³S(O)R²², -X³S(O)₂R²², -X³C(O)R²², -X³C(O)OR²²,

- $-X^3C(O)NR^{22}R^{23}$, $-X^3NR^{22}R^{23}$, $-X^3NR^{23}C(O)R^{22}$, $-X^3NR^{23}C(O)OR^{22}$,
 $-X^3NR^{23}C(O)NR^{22}R^{23}$ or $-X^3NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein X^3 is as defined
 above, R^{22} is (C_{3-6}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-6}) cycloalkyl (C_{0-6}) alkyl,
 phenyl (C_{0-6}) alkyl or hetero (C_{5-6}) aryl (C_{0-6}) alkyl and R^{23} at each occurrence
 5 independently is hydrogen or (C_{1-6}) alkyl; wherein within R^{11} any alicyclic or aromatic
 ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl,
 nitro, $-X^3NR^{12}R^{12}$, $-X^3NR^{12}C(O)OR^{12}$, $-X^3NR^{12}C(O)NR^{12}R^{12}$,
 $-X^3NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^3OR^{12}$, $-X^3SR^{12}$, $-X^3C(O)OR^{12}$, $-X^3C(O)NR^{12}R^{12}$,
 10 $-X^3S(O)_2NR^{12}R^{12}$, $-X^3P(O)(OR^3)OR^{12}$, $-X^3OP(O)(OR^3)OR^{12}$, $-X^3OC(O)R^{13}$,
 $-X^3NR^{12}C(O)R^{13}$, $-X^3S(O)R^{13}$, $-X^3S(O)_2R^{13}$ and $-X^3C(O)R^{13}$, wherein X^3 , R^{12} and
 R^{13} are as defined above;
 R^2 is hydrogen or (C_{1-6}) alkyl or as defined below;
 R^3 is hydrogen, (C_{1-6}) alkyl or as defined below; and
 15 R^4 is (i) hydrogen or (C_{1-6}) alkyl, wherein said alkyl is optionally substituted with
 cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$,
 $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$,
 $-OR^{14}$, $-SR^{14}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}R^{15}$,
 20 $-NR^{15}C(O)R^{14}$, $-NR^{15}C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-S(O)_2NR^{14}R^{15}$, $-NR^{15}C(O)NR^{14}R^{15}$ or
 $-NR^{15}C(NR^{15})NR^{14}R^{15}$, wherein R^{12} , R^{13} , R^{14} and R^{15} are as defined above, or (ii) a group
 selected from (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl (C_{0-6}) alkyl and
 hetero (C_{8-12}) polycycloaryl (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 25 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
 selected from $-R^{16}$, $-X^3OR^{16}$, $-X^3SR^{16}$, $-X^3S(O)R^{16}$, $-X^3S(O)_2R^{16}$, $-X^3C(O)R^{16}$,
 $-X^3C(O)OR^{16}$, $-X^3OC(O)R^{16}$, $-X^3NR^{16}R^{17}$, $-X^3NR^{17}C(O)R^{16}$, $-X^3NR^{17}C(O)OR^{16}$,
 $-X^3C(O)NR^{16}R^{17}$, $-X^3S(O)_2NR^{16}R^{17}$, $-X^3NR^{17}C(O)NR^{16}R^{17}$ or $-X^3NR^{17}C(NR^{17})NR^{16}R^{17}$,
 wherein X^3 , R^{16} and R^{17} are as defined above; wherein within R^9 and/or R^{10} any alicyclic or

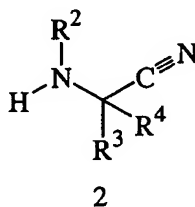
aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X³NR¹²R¹², -X³NR¹²C(O)OR¹², -X³NR¹²C(O)NR¹²R¹², -X³NR¹²C(NR¹²)NR¹²R¹², -X³OR¹², -X³SR¹², -X³C(O)OR¹², -X³C(O)NR¹²R¹², -X³S(O)₂NR¹²R¹²,
 5 -X³P(O)(OR³)OR¹², -X³OP(O)(OR³)OR¹², -X³OC(O)R¹³, -X³NR¹²C(O)R¹³, -X³S(O)R¹³, -X³S(O)₂R¹³ and -X³C(O)R¹³, wherein X³, R¹² and R¹³ are as defined above, or

R⁴ and R² taken together form trimethylene, tetramethylene or

phenylene-1,2-dimethylene, optionally substituted with hydroxy, oxo or methylene, or

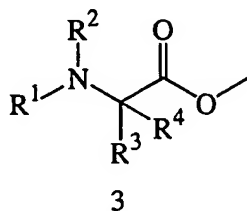
R⁴ and R³ together with the carbon atom to which both R⁴ and R³ are attached form
 10 (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof; which process comprises:

(A) reacting a compound of Formula 2:



15 or a protected derivative thereof, with a compound of the formula R¹OY, or a protected derivative thereof, in which Y is hydrogen or 2,5-dioxopyrrolidin-1-yl and each R¹, R², R³ and R⁴ are as defined above; or

(B) reacting a compound of Formula 3:



20 or a protected derivative thereof, with ammonia to provide a corresponding amide and then

reacting the amide with trifluoroacetic anhydride, in which each R¹, R², R³ and R⁴ are as defined above;

- (C) optionally deprotecting a protected derivative of a compound of Formula I to provide a corresponding unprotected derivative;
- 5 (D) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;
- (E) optionally converting a salt form of a compound of Formula I to non-salt form;
- (F) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;
- 10 (G) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;
- (H) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and
- (I) optionally converting a prodrug derivative of a compound of Formula I to its
- 15 non-derivatized form.

(19) World Intellectual Property Organization
International Bureau



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21 September 2000 (21.09.2000)

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- (74) Agents: MONTGOMERY, Wayne, W. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US).
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60/124,420 15 March 1999 (15.03.1999) US
- (71) Applicant (for all designated States except US): AXYS PHARMACEUTICALS, INC. [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): BRYANT, Clifford, M. [US/US]; 506 Richmond Drive #4, Millbrae, CA 94030 (US). BUNIN, Barry, A. [US/US]; 171 Elm Avenue, San Bruno, CA 94060 (US). KRAYNACK, Erica, A. [US/US]; Apartment E, 660 Canyon Oaks Drive, Oakland, CA 94605 (US). PATTERSON, John, W. [US/US]; 1619 Montalto Drive, Mountain View, CA 94040 (US).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/55125 A3

(54) Title: N-CYANOMETHYL AMIDES AS PROTEASE INHIBITORS

(57) Abstract: The present invention relates to novel *N*-cyanomethyl amides which are cysteine protease inhibitors, the pharmaceutically acceptable salts and *N*-oxides thereof, their uses as therapeutic agents and the methods of their making.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/06747

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C271/22 A61K31/275 A61P11/00 A61P17/00 A61P33/00
A61P35/00 A61P37/00 A61P25/00 A61P29/00 C07D209/26
C07C323/60 C07D233/26 C07D233/90 C07D277/56 C07C275/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EP0-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HANZLIK, ROBERT P. ET AL: "Reversible covalent binding of peptide nitriles to papain"</p> <p>BIOCHIM. BIOPHYS. ACTA, vol. 1035, no. 1, 1990, pages 62-70, XP000929836</p> <p>page 632; table 1</p> <p>page 627 -page 629</p> <p style="text-align: center;">--- -/--</p>	<p>1-3, 14-23</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 August 2000

Date of mailing of the international search report

17. 11. 2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bader, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/06747

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOSHIDA, HIROSHI ET AL: "Preparation of N-(2-chloroisonicotinoyl) amino acid amides as agrochemical microbicides" retrieved from STN Database accession no. 110:213341 XP002144654 abstract & JP 63 301868 A (NIPPON KAYAKU CO., LTD., JAPAN) 8 December 1988 (1988-12-08)</p> <p style="text-align: center;">---</p>	1-3, 14-23
X	<p>DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SUZUE, SEIGO ET AL: "Hepatic agents. I. Synthesis of aminoacyl (and hydroxyacyl)aminoacetonitriles" retrieved from STN Database accession no. 70:11969 XP002144655 abstract & CHEM. PHARM. BULL. (TOKYO) (1968), 16(8), 1417-32,</p> <p style="text-align: center;">---</p>	1-3, 14-23
X	<p>WO 98 01133 A (AIBE KAZUHIKO ;NOSHIRO OSAMU (JP); IGARASHI SUSUMU (JP); ISHII YAS) 15 January 1998 (1998-01-15) page 79</p> <p style="text-align: center;">---</p>	1-3, 14-23
P,X	<p>WO 99 24460 A (NOVARTIS ERFINDUNGEN VERWALTUN ;ALTMANN EVA (CH); LATTMANN RENE (C) 20 May 1999 (1999-05-20) examples 1-419</p> <p style="text-align: center;">-----</p>	1-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/06747

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-12, 33 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-12,14-35 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-12, 14-35 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12, 14-35 (all partially)

Compounds of formula I, wherein $X1=C(0)$, $R4=H$ and $R3=H$ or $R4=H$ and $R3=(C1-6)Alkyl$ or $R4=C(1-6)Alkyl$.

2. Claims: 1-12, 14-35 (all partially)

Compounds of formula I, wherein $X1=C(0)$, $R4$ is selected from subgroup (ii) and represents a functional group comprising a (poly)cycloalkyl or (poly)cycloaryl moiety.

3. Claims: 1-12, 14-35 (all partially)

A compound of formula I wherein $X1=C(0)$ and $R4$ taken together with $R2$ or $R3$ forms a cyclic structure.

4. Claims: 1-12, 14-35 (all partially); 13

A compound of formula I wherein $X1=CH_2S(0)_2$.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12,14-35 (partially)

Present claims 1-35 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or issue a complete search report over the whole breadth of the above mentioned claim(s). Consequently, the search and the report can only be considered complete for:

First subject (see suppl. sheet B):

Compounds as defined in the first invention, according to formula 1 comprising a moiety R9 as defined by claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/06747

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 63301868 A	08-12-1988	NONE	
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WO 9801133 A	15-01-1998	AU 3359697 A	02-02-1998
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WO 9924460 A	20-05-1999	AU 1487399 A	31-05-1999
		BR 9813197 A	29-08-2000
		EP 1028942 A	23-08-2000
		NO 20002320 A	04-07-2000
		ZA 9810073 A	05-05-1999
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JP 42009133 B		NONE	
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